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RIGHT VENTRICULAR HYPERTROPHY IN THE PNEUMOCONIOSIS OF COALMINERS

BY

ARTHUR J. THOMAS

From the United Cardiff Hospitals, Cardiff

Received June 12, 1950

Right ventricular hypertrophy has been recorded in the necropsy records of proven cases of coalminers' pneumoconiosis (Coggins *et al.*, 1938; Scott and Garvin, 1941; Gooding, 1946); but its frequency has not been well defined, partly because the degree of hypertrophy is not easy to establish in any particular case. The small size of the heart, clinically and radiologically, and the frequent absence in advanced cases of the classical cardiographic pattern of right ventricular hypertrophy have often caused comment (Thomas, 1948). This investigation, attempting to clarify some of these points, is presented in two parts, a pathological study of the degree of right ventricular hypertrophy present in pneumoconiosis, and a clinical study of the variation from normal of the cardiographic patterns at various stages of the disease. In some instances it has been possible to correlate the findings because the cases have appeared in both parts of the investigation.

Right Ventricular Hypertrophy at Necropsy

The hearts of fifty unselected cases of pneumoconiosis have been studied post mortem and the ventricular weights ascertained. These hearts had already been examined by a pathologist and had then been placed in formalin. The method of ventricular separation used was that described as Method B by Hermann and Wilson (1922). The auricles were removed, the ventricles were divided into sections at right angles to their long axis and then separated by dissection through the septum, and the complete right and left ventricles weighed. The normal range of the ratio of left ventricle to right ventricle, LV/RV ratio, by this method is 1·46 to 2·14 (Hermann and Wilson, 1922) and by the slightly different method of Lewis 1·57 to 2·18 (Lewis, 1914). For this study ratios below 1·40 and above 2·20 are considered to be abnormal.

The LV/RV ratios for fifty unselected cases of pneumoconiosis range from 0·61 to 2·66 with a mean of 1·16. The marked shift down the scale of this ratio is shown in Fig. 1; thirty-eight hearts have LV/RV ratios that are below the lowest limit of normal. This is a significant variation from the normal and indicates the high degree of right ventricular hypertrophy.

The mean heart weight post mortem was 361 g. with a range of 180 g. to 800 g. The ventricular weights show that the right preponderance is present even in the smallest hearts, e.g. LV/RV, 58 g./88 g., and many of the hearts in this series are small. The mean body weight of the patients was 48·1 kg. (range 29 to 71 kg.) and their mean age at death 58·4 years (range 39 to 71 years). It is possible to relate ventricular weight to body weight both in grams; the controls in the Hermann and Wilson series ranged from 0·0017 to 0·0039 and they considered ratios above 0·0050 indicative of ventricular hypertrophy. In the present series the ratio is available in 29 instances; the mean ratio is 0·0051 with a range from 0·0033 to 0·0078, and 16 have a ratio above 0·0050.

In many of the cases the right ventricular hypertrophy was visible before dissection and the right ventricle was clearly bigger than the left in some of them (Fig. 2). In others the relative

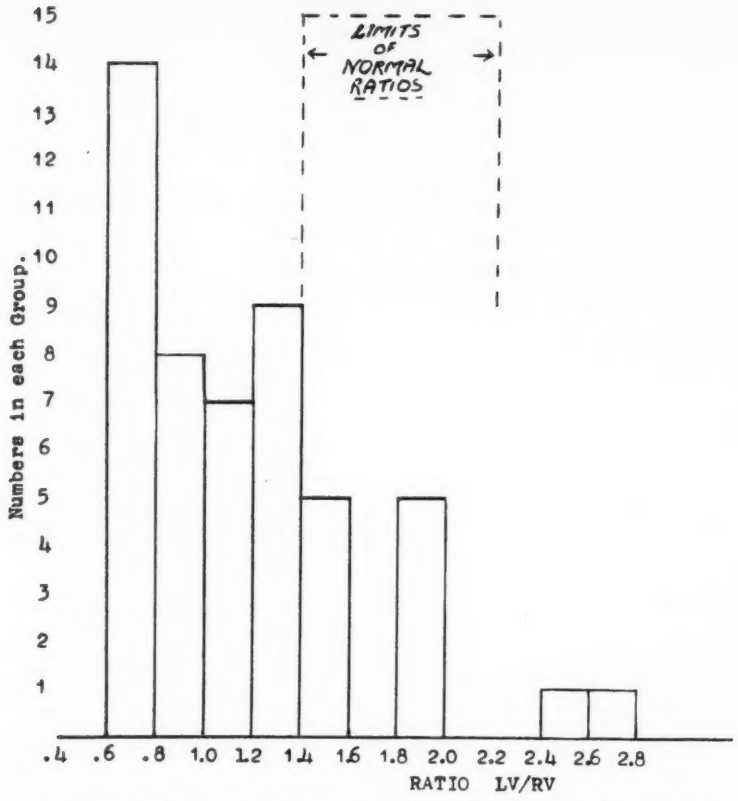


FIG. 1.—The ratio of the weights of left ventricle to right ventricle in fifty unselected cases of pneumoconiosis of coalminers.

increase in weight of the right ventricle became evident only after dissection, and often the LV/RV ratio was lower than the appearance of the whole heart suggested. The hypertrophy is first evident in the thickening of the muscle around the base of the outflow tract, and particularly the supraventricular crest. There is accentuation of all the normal features of the right ventricle so that the trabeculæ carnæ and the papillary muscles are thickened (Fig. 2 and 3). The left ventricle appears relatively small and the cavity of the right ventricle extends further into the apex of the heart than is normal.

Analysing the lung lesions and the causes of death, 30 cases had massive fibrotic dust lesions; 20 of these died of pure pulmonary heart failure, the mean LV/RV ratio of this group being 0·90 as against the mean of the series 1·16; only one had a ratio above the lower limit of normal (1·48: 1·40). Three others died of heart failure due to pneumoconiosis plus atheroma, tuberculosis, and emphysema respectively; two without heart failure died of pneumoconiosis and tuberculosis, and the remaining five with massive lesions had other unrelated diseases.

Apart from the 30 dealt with above, there were 6 deaths from heart failure without massive lesions; three of these had massive emphysema with some dust foci and an LV/RV ratio below the lower limit of normal; the other three had hypertensive heart disease, aortic stenosis, and syphilitic aortitis respectively with LV/RV ratios of 1·82, 2·57, 2·66 in that order.

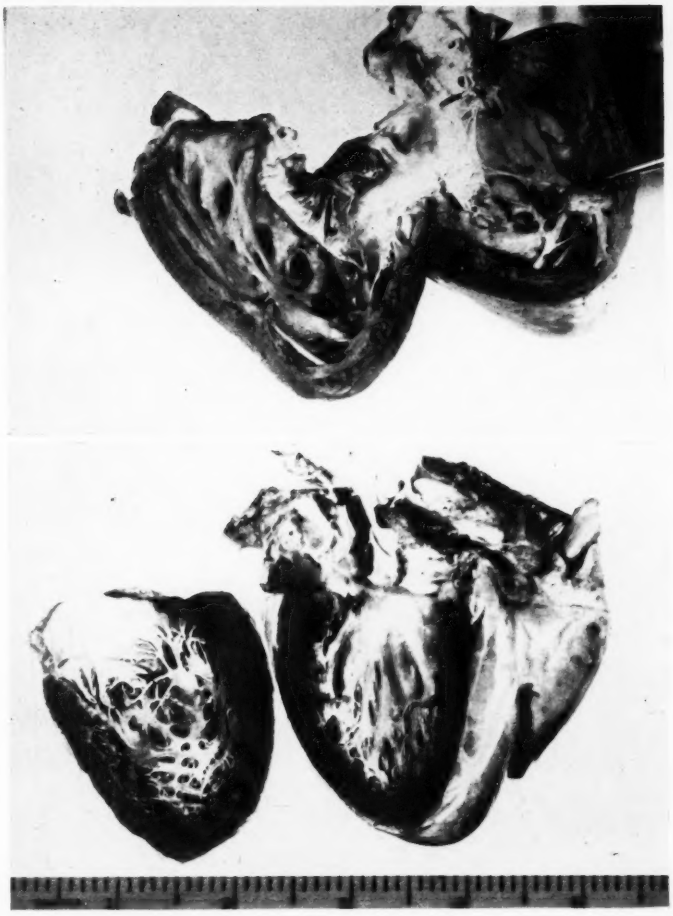


FIG. 2.—The powerful right ventricle is noted on inspection and the structures forming the outflow tract are thickened and prominent. The left ventricle appears relatively small. Case No. 167, aged 39 years, body weight 64 kg. Left ventricle 140 g., right ventricle 190 g. LV/RV=0·74.

Right ventricular hypertrophy and death from right heart failure are associated with massive fibrotic lesions in 21 cases, but with massive emphysema in the presence of focal dust lesions in only 3 cases. Furthermore, there are cases with massive fibrotic lesions dying of other diseases before heart failure appears, which show a progressively increasing degree of right ventricular hypertrophy.

There are 18 necropsies of cases that had been subjected to complete clinical and cardiographic examinations, but not all were seen in the final phase. Three deaths resulted from coronary artery disease: this had been postulated a year earlier in one patient aged 47 years; in the second there was proven cardiac infarction present some weeks before death in heart failure supervened; and in the third, followed clinically for a long period with recurring cardiac failure and cardiographic evidence of considerable right ventricular hypertrophy, the terminal event was a cardiac infarction but the gross right ventricular hypertrophy was mainly due to the massive pulmonary lesions. One

FIG. 3.—The left and right ventricles are shown after dissection to illustrate the change in size and structure of the right ventricle with advanced complicated pneumoconiosis. Left ventricle 77 g. Right ventricle 98 g. The chest lead pattern recorded a few weeks before death is shown in Fig. 6A. Case No. 339, aged 48 years.

patient had mitral stenosis and severe pulmonary disease: another presented for a long period with advanced pulmonary disease, moderate hypertension, persistent cardiac failure, and a cardiographic pattern of left bundle branch block; post mortem the heart weighed 520 g. and both ventricles were dilated.

The remaining 13 deaths were due to the pulmonary disease. Eleven died in right heart failure due to pneumoconiosis and had electrocardiographic evidence of right ventricular hypertrophy for many months before death; four of these hearts, which were weighed, gave ratios below 1·00, viz. 0·61, 0·71, 0·79, and 0·88. The other two died of emphysema and pneumoconiosis without heart failure, and the LV/RV ratios were 1·00 and 1·02: the cardiographic patterns of these two, recorded at intervals during the last two years, failed to show any right ventricular hypertrophy and radiologically the heart of one was very small, the right and left ventricles each weighing 91 g. (Fig. 4). These two show that severe pneumoconiosis and emphysema may terminate before right heart failure develops and before right hypertrophy is sufficient to appear on the chest lead pattern.

FIG. 4.

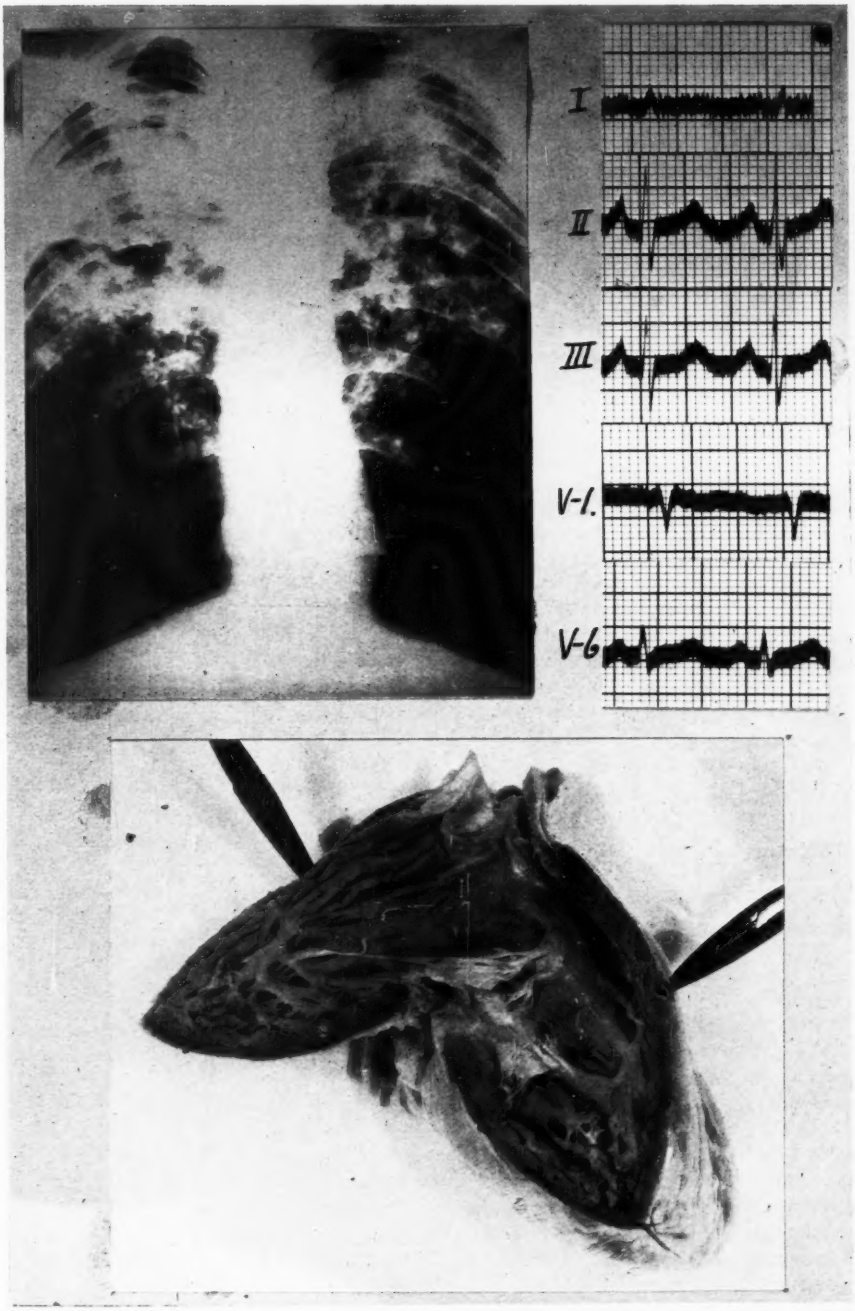
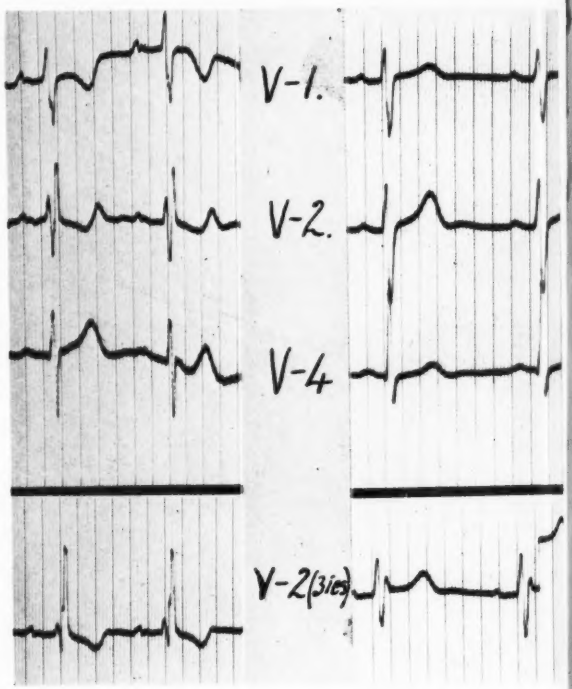


FIG. 4.—The open right ventricle is shown. Left ventricle 91 g. Right ventricle 91 g. LV/RV=1·00. This patient had complicated pneumoconiosis and massive emphysema. Case No. 348, aged 42 years.

It is suggested that the LV/RV ratio has to drop below 1·00 before the pattern of right hypertrophy can be expected.

The earlier hypertrophy is found in the walls of the outflow tract and a chest lead from the medial end of the third left interspace anteriorly has been used in an effort to detect this hypertrophy at an earlier stage. This lead is shown as V2 (3 ics.) in Fig. 5; it is abnormal in the first, normal in the second. An r′ wave higher than 4 mm. is regarded as abnormal and indicative of hypertrophy of the right ventricular outflow tract. Harris (1941) has shown that this region is one of the last to be activated and the late appearance of the r′ conforms with this fact, yet the delay, 0·07 sec., is not that of a conduction defect. The height of the r′ has been found not to exceed 4 mm. in the normal, as shown later. The presence of the abnormal r′ wave in V2 (3 ics.) has coincided with an hypertrophied outflow tract of the right ventricle in the seven cases in this series in which it was recorded.

The method of assessing ventricular hypertrophy post mortem as described above, is considered to be of value in correlating the cardiographic findings, particularly when the heart is of normal or small overall size.



A B

FIG. 5.—(A) Tracing to illustrate extreme abnormality of V2 (3ics.): the r′ pattern is present in V2 in this case. Lesser degrees of abnormality show in V2 (3ics.) when not present in V2. LV/RV=0·95. Case No. 279.

(B) Tracing to illustrate the limit of normality accepted in V2 (3ics.) This tracing is from a patient in the clinical series with complicated pneumoconiosis stage B and no other evidence of involvement of the right heart. Case No. 40, C.

RIGHT VENTRICULAR HYPERTROPHY IN THE ELECTROCARDIOGRAPH

A planned investigation of pulmonary function carried out by the Pneumoconiosis Research Unit (M.R.C.) on normal men and coalminers with all stages of pneumoconiosis has provided the opportunity for a cardiological examination of miners with pulmonary disease. This part is principally concerned with the results of the electrocardiographic investigations. The tracings were taken with the patient reclining at an angle of 45 degrees, standard limb leads, CR chest leads, and V chest leads being recorded with an instrument that gave three simultaneous traces. The subject then performed a standard amount of work—700 kg.m.—in the form of a two minute stepping test. The CR chest leads were recorded again at the termination of the test with the subject reclining. Then followed a cardioscopic examination and later a study of the standard chest radiographs. In all, 146 persons were examined, representing all the age groups, normals, and disease categories. The classification of the pneumoconiosis is that described by Fletcher *et al.*, 1949.

There were 44 normal men, of whom 16 were miners. The cardiographic findings conformed

closely to the normal series of Myers *et al.*, 1947 and of Sokolow *et al.*, 1949. The findings in 25 of these of ages comparable to the disease groups are given in Table I.

Forty-one patients with simple pneumoconiosis have been examined. Three had some evidence of left ventricular prominence and one other had paroxysms of auricular fibrillation; these findings were not related to the pulmonary disease. The remainder presented cardiographic patterns of normal form. In three instances there was respiratory variation of considerable degree in the tracings, especially after exercise, and in nine there was an increase in the height of the T wave after exercise. No suggestion of right ventricular hypertrophy could be found in this group.

TABLE I

ANALYSIS OF LEADS V I AND V 6 GIVING THE MEAN AMPLITUDES OF R AND S, AND IN BRACKETS, THE STANDARD DEVIATIONS

Lead	Group	R wave	S wave
V I	25 NORMALS, Group N	4·4 mm. (2·1)	12·0 mm. (4·6)
	25 ABNORMALS, Group D	4·4 mm. (2·1)	13·3 mm. (5·8)
V 6	25 NORMALS, Group N	15·9 mm. (5·2)	1·06 mm. (1·5)
	25 ABNORMALS, Group D	10·0 mm. (3·9)	1·9 mm. (1·4)

There were 24 persons with complicated pneumoconiosis, Stage B, with massive shadows present in the chest radiographs. Four only had any evidence of cardiovascular abnormality and were classed as borderline cases of right heart involvement due to the pulmonary disease. Two of these had high resting pulse rates, which increased considerably on exercise, and marked respiratory variation in the cardiograph, especially in the right chest leads. One other had a CR1 suggesting right heart involvement and also considerable variation with breathing; the last subject with a doubtful CR1 pattern presented slight enlargement of the right ventricle on cardioscopic examination.

The last group to be considered contains 25 cases of complicated pneumoconiosis, Stage D, coalminers with advanced massive shadows, pulmonary distortion, and considerable emphysema. These patients were incapacitated with gross dyspnœa on effort, and the lung function studies revealed severe impairment; 9 of these had clear evidence of right heart involvement and a further 5 were borderline cases.

Comparison of the cardiographs of this group and an equally balanced group of normal men with ages ranging from 35 to 60 years is given, the normals for convenience are labelled group N and this group is D. The P waves of lead II in the normal group have a mean amplitude of 1·7 mm. and none exceed 3 mm.: in group D the mean amplitude is 2·3 mm. and in 2 records exceeds 3 mm. Lead III shows little difference between the groups either in P, QRS, or T forms. The more frequent vertical heart pattern in group D tends to lower the R wave in lead I.

The leads from positions C1 and C6 best represent the overall chest lead pattern and details of the V leads are given (Table I). The chief significant differences between the groups are the reduction in amplitude of the R wave and the increase in amplitude of the S wave in V6 in group D, changes that are statistically significant in this series. This change in V6 has been noted by other workers (Sokolow, 1949).

In all subjects a V chest lead from the inner part of the left third interspace anteriorly has been recorded, it is called V2 (3 ics.). In the normals the pattern resembles V2; in six traces there is an rSr′ pattern, the highest r′ being 4 mm. and the mean height 2·2 mm. In group D the r′ was present in 9 instances with a mean height of 6·2 mm., and a range from 2 mm. to 16 mm., a significant difference. The peak of the r′ wave falls an average of 0·07 sec. after the start of the QRS deflection and the r′ wave is not due to a conduction defect. The suggestion made earlier that the abnormal r′

wave in V2 (3 ics.) is useful evidence of hypertrophy of the right ventricular outflow tract is supported by these findings.

The recording of cardiograms at rest and immediately on terminating a standard exercise test revealed considerably higher resting rates in group D and a greater increase in rate with the same amount of exercise; thus a resting rate of 90 a minute with an increase to 115 a minute on the standard test, was not uncommon. Variations in the contour of the QRS can occur normally with breathing, but in complicated pneumoconiosis there is a much greater respiratory variation particularly in CR1 where the mean measured difference showed that group D had twice the degree of respiratory variation seen in the normals (Fig. 6). This curious phenomenon is under further study at present.

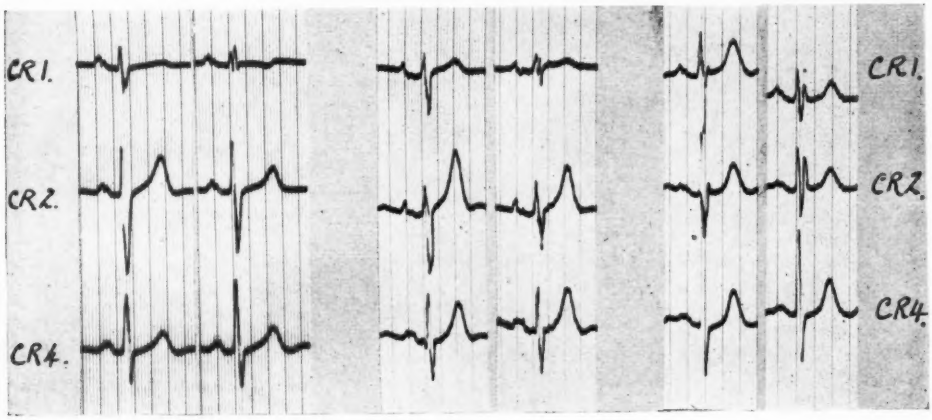


FIG. 6.—Chest leads CR1, CR2, CR4 illustrate the change with respiration. In CR1 and V1 on inspiration the S wave lessens in amplitude, the R wave simultaneously increases and the T wave lessens or inclines to negativity. The r′ becomes prominent in (C). The three traces are recorded simultaneously. Case Nos. 339, 310, 51.

This graded series of miners, from normal men through the categories of simple pneumoconiosis to the most severe degree of complicated pneumoconiosis, shows no striking cardiographic change and that found is mainly in the most severe Stage D. Here the first change is in V6, a reduction of the R wave, an increase in the S wave. An occasional cardiographic pattern of classical right ventricular hypertrophy is found in Stage D. Also in Stage D an r′ wave above normal amplitude in V2 (3 ics.), is rather frequent, a finding that is helpful in the diagnosis of outflow tract hypertrophy on the right side.

The increased resting pulse rate and the further abnormal increase in the rate with moderate exercise are not an indication of ventricular hypertrophy, but of a compensatory mechanism called forth by the effect of severe pulmonary disease on the heart.

Respiratory variation of the cardiogram is a normal finding but is here found in abnormal degree in the right chest leads in abnormal cases, and surprisingly in those whose chest wall and diaphragmatic movement are restricted. It is well known that there is respiratory variation of the peripheral arterial pressure, and several workers have demonstrated changes in the ballistocardiogram on respiration (Otis *et al.*, 1946). The electrocardiographic variation must be presumed to be due to positional changes for the present, but certain features justify further study. The same may be said of the increased height of the T wave after exercise which is most marked in the severe cases; clearly tachycardia is partly responsible but does not account for the total increase in some of the severe cases.

The relationships between the cardiological findings and the lung function studies must be the subject of another report. In general, there is over 50 per cent impairment of lung function in those patients who are found to have right ventricular hypertrophy, but there are also patients without evidence of hypertrophy who have the same impairment of lung function. It would seem that the duration of the severe stage of lung disorder is operative in addition to the degree of the disorder.

Clinically it may be said that evidence of right heart involvement is most uncommon in the pneumoconiosis of coalminers, until the disease is complicated and there is progressive massive fibrosis with emphysema and distortion. The pathological studies have shown the great degree of right ventricular hypertrophy usually found in these advanced cases, and have forced us to the admission that the electrocardiographic patterns are a poor test of early right ventricular hypertrophy. An effort has been made in this work to improve the cardiographic diagnosis of hypertrophy by assessing the changes in V1 and V6 and also by the introduction of V2 (3 ics.). Certain other pointers to the severity of the right heart stress are the increased resting pulse rate and the further increase on a standardized exercise test. The circulatory effects of respiration, both normal and abnormal, still require further elucidation.

Summary

A series of 50 hearts from cases of coalminers pneumoconiosis have been dissected and the ventricular weights recorded. The ratio of left ventricle to right ventricle, LV/RV ratio, shows a great reduction, and there is a consistent relative increase in the weight of the right ventricle.

A cardiographic study of 146 persons (normal men, miners and non-miners, and patients with all stages of pneumoconiosis) has shown that V6 changes most with increasing severity of lung disorder. In the most severe groups the R wave of V6 is diminished and the S wave is increased in amplitude. A suggestion is made that a lead from the third interspace immediately above V2 may help in the diagnosis of right ventricular hypertrophy when it shows an r′ wave of 4 mm. or more in height.

Certain effects of respiration on the electrocardiogram are described, particularly the respiratory variation of the chest leads on the right side. This is presumed to be a positional change, but some findings suggest that the mechanism of respiratory variation should be further investigated in relation to respiratory function.

I wish to express my appreciation and thanks to Dr. C. M. Fletcher, Director of the Pneumoconiosis Research Unit (M.R.C.), Llandough Hospital, for permission to study the cases under his care and to his colleagues and staff for all their help. I should also like to thank Professor J. Gough, Department of Pathology and Dr. W. R. L. James for access to their records and for their help in providing the specimens for part of this study. I am indebted to Mr. A. Griffiths, cardiographic technician, for his assistance with cardiography and photography.

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THE Q–T INTERVAL IN RHEUMATIC DISEASE IN CHILDREN*

BY

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From the St. Francis Sanatorium for Cardiac Children, Roslyn, L.I., New York

Received December 1, 1949

The diagnosis and evaluation of cardiac involvement during the course of acute rheumatic fever has long been one of the difficult problems in medicine. Although acute rheumatic carditis is the most important manifestation of rheumatic fever, few criteria have been established for arriving at a decision as to when carditis is present and when it has finally come to an end. There are even fewer criteria for evaluating the extent of total cardiac damage that might result from an episode of acute carditis. It must be admitted that the current laboratory aids inclusive of the commonly accepted electrocardiographic criteria have been disappointing in determining the presence and measuring the extent of the inflammatory process in the heart muscle during the course of the acute rheumatic episode.

In recent months there has been a renewed interest regarding the value of the measurement of electrical systole (QT interval) in the diagnosis of rheumatic carditis. In a recent publication (Taran and Szilagyi, 1947) we have shown that the duration of the QT interval is abnormally prolonged in patients having acute rheumatic carditis. Furthermore, the abnormal prolongation of the QT interval in these patients was shown to be a function of the severity of the carditis and not that of the cardiac rate. The more severe the clinical carditis, the longer the electrical systole relative to diastole. It was suggested that this disturbance in the sequence of electrical events in the cardiac cycle was a characteristic of carditis and might be used as a valuable diagnostic criterion for the recognition of carditis in rheumatic patients. These findings have been corroborated by Abrahams (1949).

It is the purpose of this paper to present further evidence in support of this contention, and in addition to present evidence that a careful study of the changes in the duration of electrical systole may be helpful in evaluating the extent of cardiac damage resulting from acute rheumatic carditis in children.

Material and Method of Study

A group of one hundred and forty children, six to sixteen years of age were observed under controlled conditions at the St. Francis Sanatorium for Cardiac Children. One hundred and twenty-three were studied during a single period of residence at the sanatorium, the average period of observation per patient being about twelve months. The remaining seventeen patients of the group studied were observed during several periods of residence at the sanatorium and were followed for a total period of several years. The average period of observation of this group was about four years per patient.

All electrocardiographic readings were made by the same examiner using the method already described (Taran and Szilagyi, 1947). The cardiographer was not familiar with the clinical findings

* Read before the III Inter-American Cardiological Congress, June 16, 1948, Chicago, Illinois, U.S.A.

at the time of the electrocardiographic reading. The QT interval was corrected for cardiac rate according to Bazett's formula. All clinical observations were made by another examiner following rigidly the same criteria during the entire period of observation. The evaluation of progressive cardiac disability was based upon the clinical evidence of valvular damage, Roentgen measurements of cardiac size and clinical evaluation of the functional capacity according to the criteria of the New York Heart Association (1939). The diagnosis of rheumatic activity was based upon unequivocal and generally accepted laboratory and clinical criteria.

Since it is well known that the duration of the electrical systole (QT interval) may be modified by various types of medication, all patients receiving digitalis, mercupurin, salicylates, or quinidine were excluded from this study. Furthermore, since other conditions such as hypocalcæmia, acidosis, and pericardial effusion are known to modify the duration of the electrical systole, such cases were not included in this study. Patients showing crude disturbance in rhythm such as paroxysmal auricular fibrillation, flutter, and tachycardia and those showing high degrees of conduction disturbance were also not included in the present study.

Results

Group 1. Children Observed During a Single Period of Residence at the Sanatorium (Fig. 1).

Of 123 children who were observed for an average period of twelve months, 33 had a normal, or slightly or moderately prolonged electrical systole at the time of admission but all of these showed a gradual and significant shortening of the electrical systole during residence at the sanatorium. The QT interval on discharge was significantly shorter than at the time of admission. Two-thirds of these 33 children showed unequivocal evidence of rheumatic carditis. On the other hand only one in every five showed palpable evidence of progressive heart disease at the end of the period of observation. None of the 33 showed severe cardiac damage or congestive failure, and none died.

The duration of the electrical systole of 39 children of the group of 123 did not change during the entire period of observation. It was of normal duration or slightly prolonged in 13; only one of these showed evidence of rheumatic activity and one showed progressive heart disease during the period of observation. The remaining 26 children had a moderately or markedly prolonged electrical systole: all except one of these showed unequivocal evidence of active carditis and 13 had evidence of progressive cardiac disability at the end of the period of observation; none had congestive failure and none died.

The remaining 51 children of the group of 123 showed a progressive prolongation of the electrical systole from the time of admission to discharge. At the time of admission 11 of these showed QT intervals of normal duration and no evidence of rheumatic activity; at the end of eleven months of observation all were mildly active and four of these developed evidence of progressive heart disease. Forty children had a prolonged electrical systole at the time of admission and a significantly longer electrical systole at the end of the period of observation; more than three-fourths of this group (31) showed evidence of progressive heart damage. Of greater significance is the observation that of the 20 children in this group who had a markedly prolonged QT interval on admission, all except one showed severe and progressive heart damage; two developed auricular fibrillation, three developed congestive failure, and four died.

These observations suggest a close association between the abnormal prolongation of the electrical systole and the occurrence of progressive heart disease during the course of acute carditis. When the QT interval is abnormally prolonged and becomes longer during the course of rheumatic carditis, a high degree of associated cardiac damage may be expected. Furthermore, a marked prolongation of the QT interval that does not show a tendency to become shorter is frequently associated with evidence of progressive heart damage. Finally, patients who show a significant shortening of the abnormally prolonged electrical systole during the course of carditis usually present little evidence of progressive heart damage.

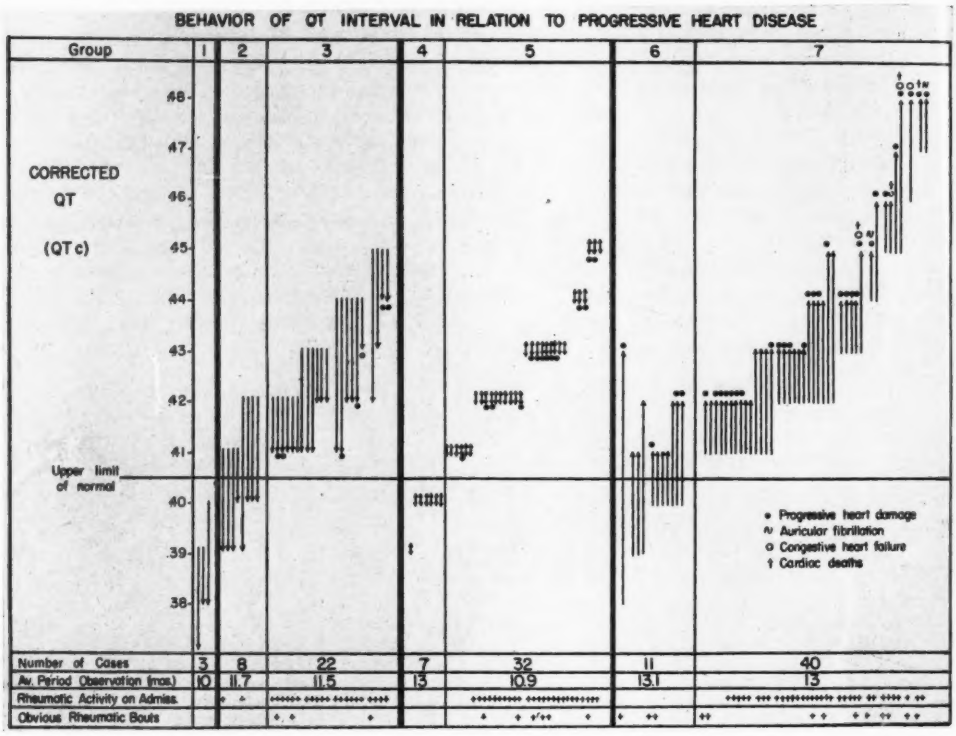

FIG. 1.—The figure is a graphic representation of the relation of the duration of the electrical systole to progressive heart disease observed during a single period of residence at the sanatorium. Each line represents a case; the arrow point represents the duration of the QTc at the end of the period of observation and the other end of the line represents the duration of the QTc at the beginning of the period of observation.

Group 2. Children Observed over Several Years Duration (Fig. 2).

The children of this group were observed carefully for a total of sixty-seven patient years. The periods of residence at the sanatorium were interrupted by short periods of home care, of follow-up at a clinic, or of admission to hospital.

Of this group of seventeen children, nine, who were observed over a total period of thirty-six patient years, showed no or minimal cardiac damage. All of these had definite rheumatic bouts but only a slight prolongation of the electrical systole at any time during the entire period of follow-up. In most cases the duration of electrical systole showed a tendency to decrease rather than increase. The remaining eight children who were observed over a total period of thirty-seven patient years showed moderate to severe progressive heart disease and all of these demonstrated moderate to marked prolongation of the electrical systole at any time during the period of observation with a distinct tendency for the QT interval to become longer from the beginning to the end of the period of observation.

In the children of Group 2, a high degree of correlation exists between the prolongation of the electrical systole and progressive cardiac disability. In addition, this group demonstrates that the time factor may also play a significant role in bringing about this close correlation. The longer the

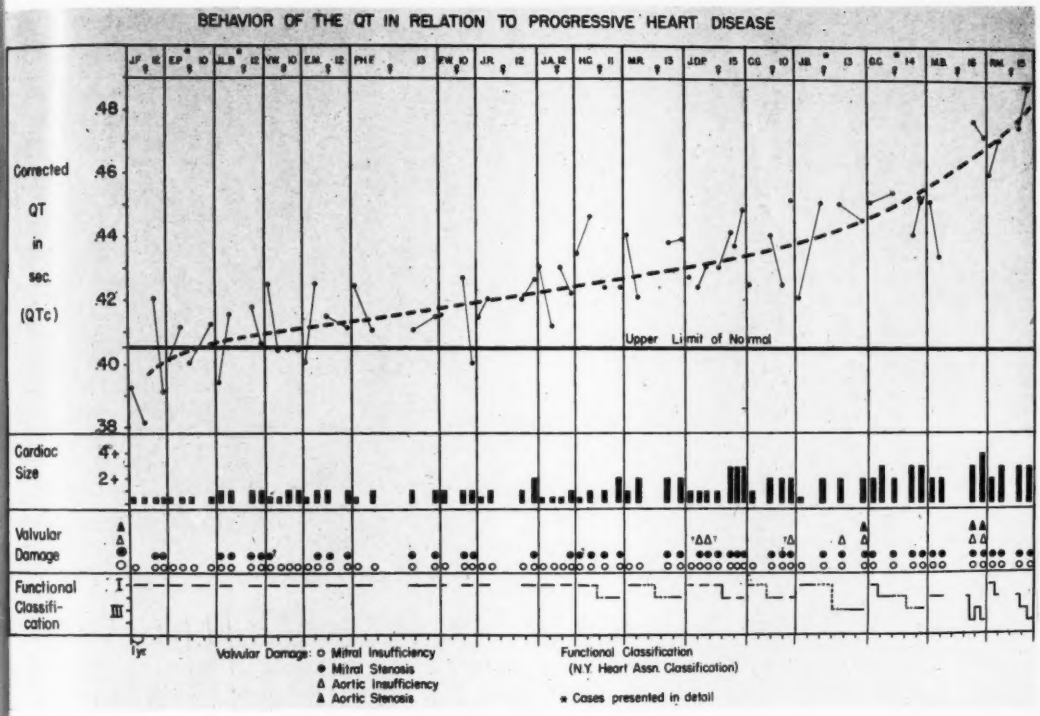

FIG. 2.—This figure is a graphic representation of the relation of the duration of the electrical systole to progressive heart disease observed over several years duration. The broken ascending line represents the average duration of the QTc of each individual case. The lines crossing the ascending line represent the longest and shortest QTc for each period of residence at the sanatorium.

period during which the electrical systole remains prolonged, the more likely and the more severe the total cardiac damage.

This parallelism between the duration of the electrical systole and progressive cardiac disability becomes even more evident from a detailed study of individual cases (Fig. 3, 4, 5, and 6).

COMMENT

There has always been unanimous agreement among physiologists that a prolongation of systole relative to diastole is a manifestation of impairment of the functional integrity of the myocardium. Wiggers and Clough (1919) found consistently that prolongation of systole was significant of functional cardiac disorder. Katz (1929) suggested that the prolongation of systole in a diseased heart as compared with a normal heart would constitute a measuring rod for determining the functional integrity of the myocardium. Bazett (1920) was of the opinion that the duration of systole in a diseased heart may be used as a measure of active cardiac dilatation. Tung (1941) arrived at the same conclusion.

The evidence presented in this study would seem to concur completely with the above mentioned observations. One of the expressions of the disturbed cardiodynamics present in acute rheumatic heart disease is a prolongation of systole relative to diastole. The more extensive the carditis and, therefore, the greater the disturbance in the functional integrity of the myocardium, the longer is the

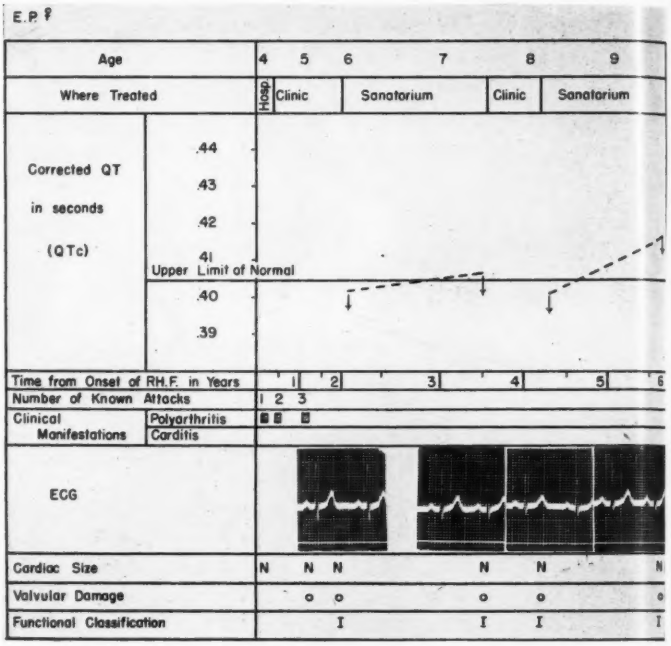

FIG. 3.—This figure illustrates the history of a patient observed over a period of six years. The patient had had three attacks of polyarthritis between the ages of four and five years and has had no recurrences since.

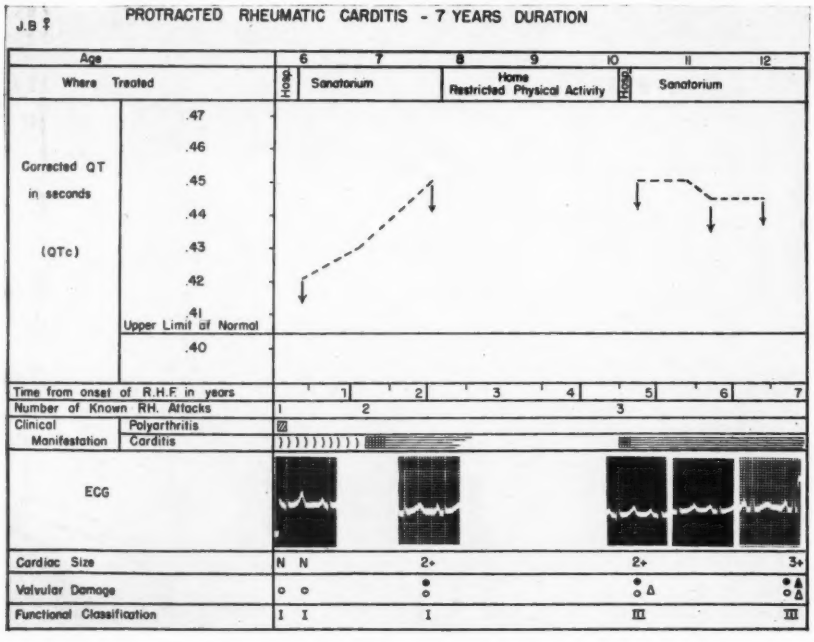

FIG. 4.—This figure illustrates the history of a patient who was observed for a period of seven years. The onset was with polyarthritis and this was followed by a mild carditis; from the age of seven years to the present time the carditis has persisted.

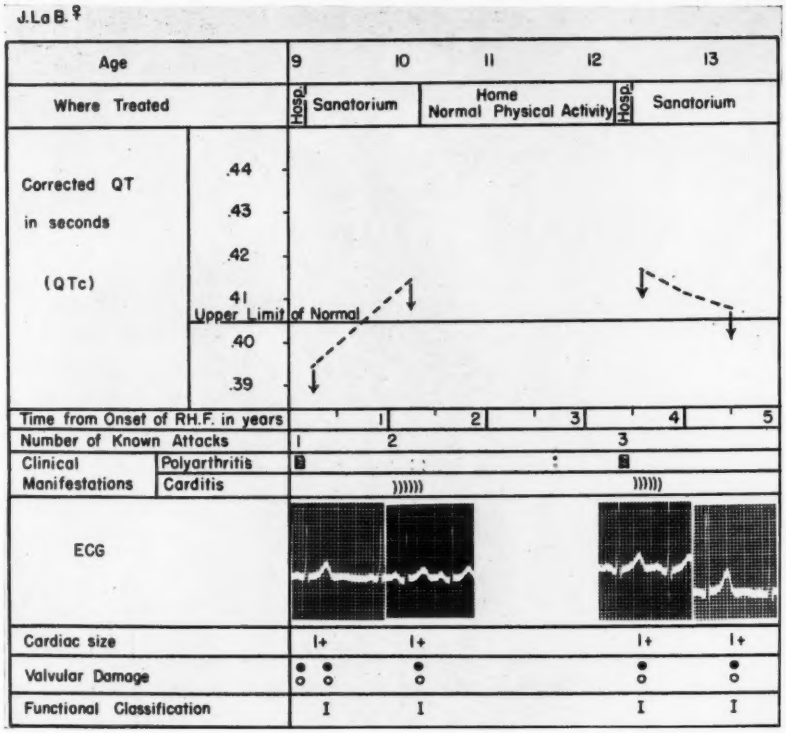

FIG. 5.—This figure illustrates the history of a patient who was observed for a period of five years. The patient had one attack of polyarthritis at nine years of age, a mild attack of carditis at ten years of age, and another attack of polyarthritis at twelve years of age followed by a mild carditis. Each of these attacks was of short duration.

Age is represented in years. The broken line represents the readings of the duration of the QTc at various intervals. The arrows point to the electrocardiograms represented on the chart. Functional classification in accordance with Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, 1939.

Cardiac size is represented as follows:
N =normal size
1+ =slightly enlarged
2+ =moderately enlarged
3+ =markedly enlarged
4+ =marked enlargement in all diameters

Valvular damage is represented as follows:
○ =mitral insufficiency
● =mitral stenosis
△ =aortic insufficiency
▲ =aortic stenosis

electrical systole relative to diastole. The observations presented in this paper further indicate that there is a close correlation between the degree of prolongation of electrical systole and total cardiac damage. Finally, our observations suggest strongly that the longer the period during which the normal relationship of systole to diastole is disturbed, the greater the total cardiac disability resulting from rheumatic carditis. While this study does not postulate a cause and effect relationship between the prolongation of the electrical systole and progressive heart disease, the evidence clearly leads to this implication. Further exploration in this direction is now in progress.

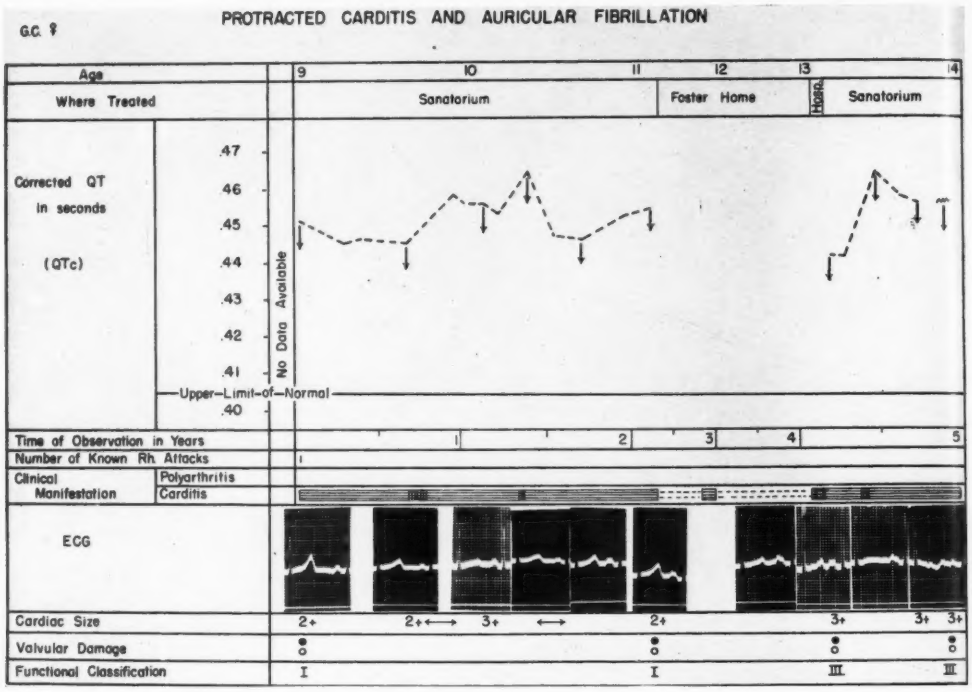

FIG. 6.—This figure illustrates the history of a patient who was observed over a period of five years. The patient had protracted carditis fluctuating between moderate and severe during the entire period of observation.

SUMMARY AND CONCLUSIONS

One hundred and forty rheumatic boys and girls, six to sixteen years of age, were observed during a total period of almost one hundred and eighty patient-years.

The duration of the electrical systole (QT interval) was studied in these children in relation to progressive heart disability.

A close correlation existed between the duration of the QT interval and the extent of cardiac disability resulting from acute rheumatic carditis.

It was further observed that the longer the time during which the electrical systole remained abnormally prolonged, the more extensive the total cardiac damage.

It is postulated that this disturbance in the normal sequence of events in the cardiac cycle in acute rheumatic carditis in children may be used as a valuable aid in prognosticating the extent of cardiac damage resulting from carditis.

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ELECTROCARDIOGRAPHIC PATTERNS IN SLIGHT CORONARY ATTACKS

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The seriousness of cardiac infarction can be assessed on clinical grounds. Prolonged pain refractory to morphia, severe shock with fall of blood pressure to dangerous levels, and the early onset of cardiac failure are unequivocal signs of a severe attack. In many patients regarded as suffering from cardiac infarction there are none of these signs, and the diagnosis is based on coronary pain accompanied by electrocardiographic changes of acute myocardial ischæmia. Were it not for the persistent electrocardiographic signs such attacks would be more suggestive of prolonged bouts of angina at rest than cardiac infarction proper. The clinical term " slight coronary attack " applied to this condition seems thus appropriate, for the symptoms are slight and the name disregards the problematic existence of actual thrombosis and myocardial necrosis. Slight coronary attack implies cardiac pain for half an hour or more, arising at rest and not relieved by trinitrin, always accompanied by persistent electrocardiographic signs of myocardial ischæmia but not by the clinical and laboratory signs of extensive myocardial necrosis (Papp, 1949)

Similar conditions have been variously described. " Coronary insufficiency without occlusion " is the term used by Master (1946) for a condition more severe than angina of effort but lighter than acute myocardial infarction—for the latter he proposes the name " acute coronary insufficiency with acute occlusion ". He lists a great number of exciting causes restricting coronary blood flow and responsible for the attack. But these have only exceptionally played any part in our series, in which the attacks were as sudden and devoid of cause as in the classical acute coronary occlusion. " Coronary failure " is the name given by Freedberg, Blumgart, Zoll and Schlesinger (1948) for the " clinical syndrome intermediate between angina pectoris and acute myocardial infarction ". This syndrome is of wide range and comprises some of our cases. However, in coronary failure the electrocardiographic changes are slight or absent, except in the more severe cases where they may persist for hours and then revert to normal. This was not so in the majority of our series where a diagnosis of cardiac infarction was made on the basis of persistent electrocardiographic changes showing the initial signs of acute myocardial ischæmia with subsequent serial changes typical of such lesions for weeks or months after the acute attack.

The purpose of the present investigation is, first, to determine the incidence of slight coronary attacks and how far there is an agreement between the slight clinical and electrocardiographic features ; secondly, to investigate the prognosis of the attack and the incidence of the early complications, and thirdly, to draw conclusions regarding treatment.

Material and Method of Investigation

A clinical analysis has been made of one hundred and nine consecutive patients with a diagnosis of cardiac infarction. They consisted of 63 hospital in-patients, 24 patients seen in consultant practice, and 22 seen in general practice. No case first seen more than a fortnight after the acute

attack was included, nor any in whom there were less than two confirmatory electrocardiograms. Among these 109 cases there were 33—little less than one-third—in whom no shock or cardiac failure followed the attack. These were regarded as having had slight coronary attacks ; 12 were hospital in-patients, 12 were seen in consultant practice, and 9 in general practice. Thus patients with slight coronary attacks were almost twice as frequent outside as inside hospitals. Ages ranged from 42 to 73 years, with the greatest incidence between 50 and 69 (24 patients); two were over 70. The proportion of men to women was three to one (Table I).

TABLE I

AGE AND SEX IN 33 PATIENTS WITH SLIGHT CORONARY ATTACKS

Age :	40–49	50–59	60–69	70–73	Total
Males :	7	9	7	2	25
Females :	—	2	6	—	8

Proportion of men to women = 3 : 1

CLINICAL ANALYSIS OF SLIGHT CORONARY ATTACKS

Pre-existing conditions. Angina of effort was complained of in 17 ; it had existed for more than two months in 12, and for less than two weeks in 5, where it followed the acute attack. In addition, 6 further patients developed angina after their coronary attacks ; this brings the total number of patients suffering from angina to 23. Coronary thrombosis had been diagnosed in five previously ; in three, who were seen during these attacks, they were slight. There were 10 hypertensives, 4 diabetics, and 3 obese patients in the series ; obesity, diabetes, and angina of effort coexisted in three. Two were chain-smokers and one had intermittent claudication ; in only two had there been no previous symptoms or associated disorders.

Pain. Prolonged attacks suggesting coronary occlusion were present in 27 cases. In these, the pain lasted from one to twelve hours. In longer lasting attacks, the pain was intermittent ; it was difficult to form an accurate judgement of the intensity of pain, but the fact that only half of the patients with attacks longer than one hour required morphia is inconsistent with extreme pain. With one exception (Case 9, Fig. 9) a single injection of morphia (gr. 1/4 to 1/3) suppressed the pain. The onset of pain was sudden and mostly occurred at night during sleep ; in four it started while the patient was walking. Major physical effort could be held responsible only in two ; in Case 9, the pain started while the patient was dancing after a heavy meal ; in Case 6 (Fig. 6), while he was cranking a car. In Case 22 it began under spinal anæsthesia during investigation for intermittent claudication. The spread and quality of pain were characteristic of cardiac infarction. Anginal pain frequently recurred during the period of observation ; it rarely required injection of morphia and was usually abolished by trinitrin or pethidine tablets. In six patients who had no longer lasting bouts of pain, the attacks were those of angina of effort or at rest and none of them required morphia ; in these the diagnosis was based on the electrocardiogram only. Severe angina of effort following the acute attack, not the attack itself, was the reason why medical help was sought in three patients.

Fall of blood pressure was irrelevant in most. The systolic blood pressure was never less than 100 and only in five was it from 100 to 110 for a short time. The diastolic blood pressure was well in proportion with the systolic, and the pulse pressure never fell below 30.

Pulse rate was normal and the rhythm regular in all during the period following the attack. Two patients, while having the attack, had regular ectopic tachycardia ; Case 9, with a rate of 160, Case 21, at a rate of 176.

Pyrexia was found in five. In Case 14 it lasted for five days ; in the others, one to three days, with a maximum of 101° F.

White cell count was raised to 9500 in Case 13. In seven other patients, seen sufficiently soon after the attack, it was normal. Blood sedimentation rate was raised in five instances to a maximum of 32 in the hour, and was normal in seven.

Course. The clinical course was uneventful and all the patients recovered from the acute attack. There were no pulmonary or embolic complications during the two-months period of close observation, but Case 9, eight months later, had a cerebral embolism from which he recovered. Cardiac enlargement with evidence of slight failure was seen in Case 15, an obese diabetic, two years after he had the first slight coronary attack. In all the others the heart size was normal on radioscopy except for a few patients with slight left ventricular hypertrophy consistent with coexistent hypertension. Angina of effort in more or less severe degree or short attacks of angina at rest were frequent features ; they were present in 23 out of 33 patients during the period of observation lasting from two months to over three years.

Electrocardiographic Features

Electrocardiograms recorded following 35 slight coronary attacks (Cases 8 and 15 were seen in two attacks, both slight) showed the following patterns of myocardial ischæmia (Table II).

TABLE II

Electrocardiographic Analysis of 35 Slight Coronary Attacks

	(17) Ant. septal	(7) Ant. lateral	(2) Ant. apical	(6) Post.	(3) Post. lateral	(35) Total
R small or abs.	3	—	—	—	—	3
Q present	3	1	1	2	—	7
EC restored	7	4	—	2	1*	14
EC improved	9	1	1	3	—	14
EC unchanged	1	2	1	1	1	6
EC worse	—	—	—	—	1	1

*Varied from normal to abnormal.

Anteroseptal, with changes in leads V_1 to V_6 with main changes in leads V_2 to V_3, in 17 instances (Fig 1, 2, 3, 5 and 7).

Anterolateral, with changes in leads V_4 to V_6, in 7 instances (Fig. 4).

Antero-apical, with changes in V_4, in 2 instances (Fig 6 and 8).

Posterior, with changes in leads II, III and AVF, 6 instances (Fig. 10, 11 and 12).

Posterolateral with changes in leads III, AVF, V_5 to V_7, in 3 instances (Fig. 9).

According to the position of the heart, the anteroseptal and anterolateral changes were carried into leads AVL and I, rarely into AVF. On the whole, the unipolar extremity leads were of little help in the diagnosis of these patterns and could be dispensed with.

Abnormality of R–T or T wave patterns were prominent in all records and consisted of high take-off, coving of R–T and deep T inversion in one or more leads. When these changes were conspicuous in V_2 to V_4, as they always are in anteroseptal ischæmia (Fig 1, 2, 5 and 7), they faintly recalled the ones found in right ventricular hypertrophy and in localized pericarditis. There was no reason to assume that either of these conditions existed in our patients, since no case of pulmonary infarction accurred in our series nor was pericardial rub ever heard. On the other hand, there was great similarity between our records of anteroseptal ischæmia and those of Brock and Campbell (1950) found during the healing stage of right ventricular wounds in patients operated on for pulmonary stenosis. Current of injury was recorded once (Case 3, Fig. 3). The R wave was

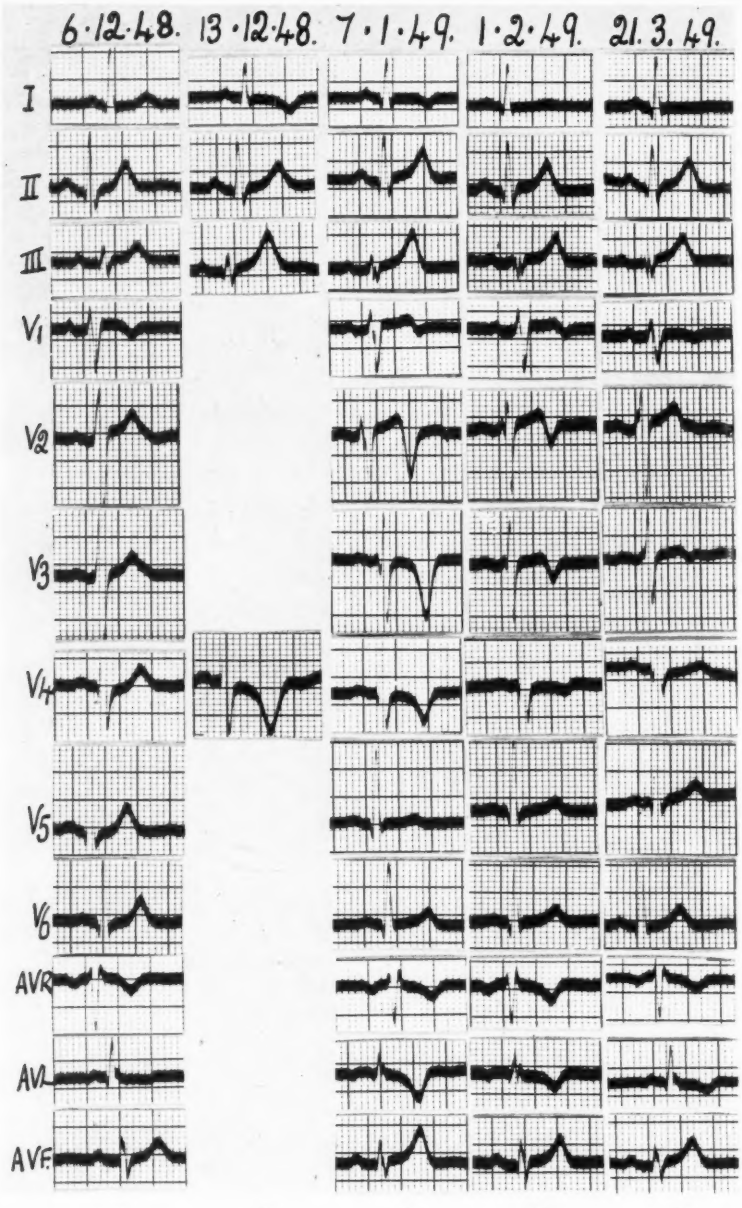

FIG. 1.—Case 1. Man, aged 52. Four years angina of effort. Coronary attack 4 days previously followed by frequent angina at rest. No pyrexia, normal E.S.R., insignificant fall of B.P. Still occasional angina. Records show anteroseptal ischæmia. (A) Normal record 3 days prior to attack. (B) Inversion of T in I with reciprocal elevation in III, deep inversion of T in V4 with cove-shaped S–T, 4 days after attack. (C) Changes in 12-lead record involve V2–V4 and AVL with reciprocal effect in III and AVF. (D) Gradual disappearance of abnormalities. (E) Restoration to near normal after 3½ months ; note increase of R in V2 and AVL.

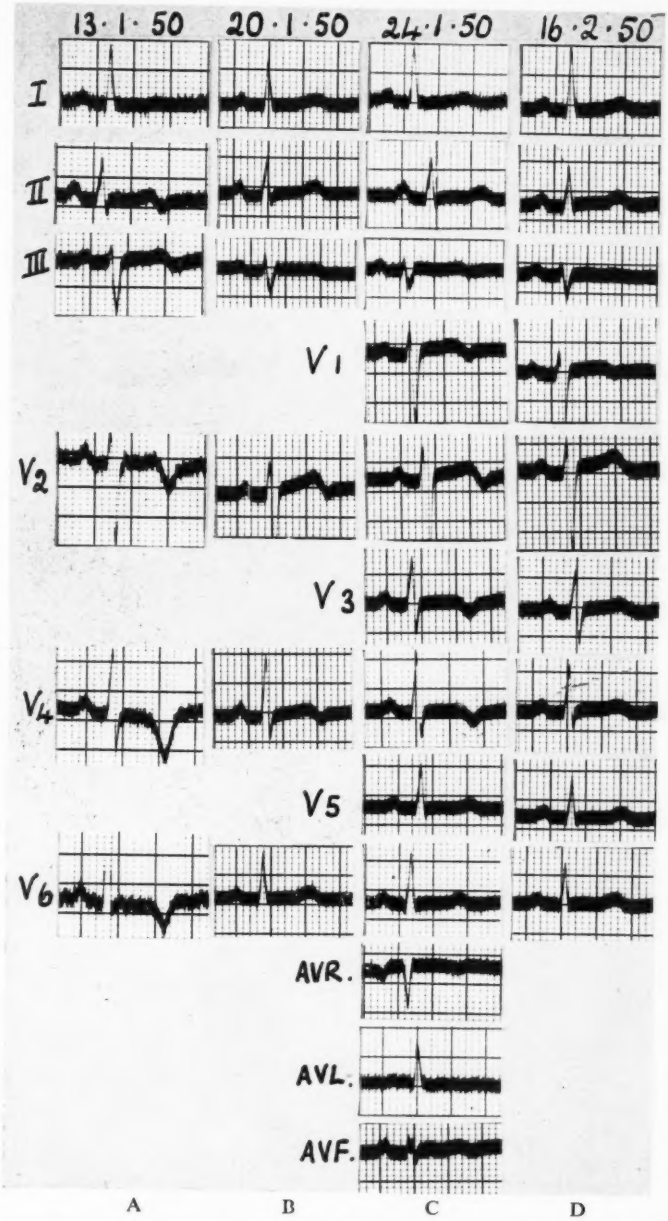

FIG. 2.—Case 2. Woman, aged 56. Coronary attack for 1½ hours three months previously followed by disabling angina of effort. Rest for 4 weeks then gradual resumption of work. Records show anteroseptal ischæmia. (A) Little change in limb leads, deep T inversion V2–V6, cove-shaped S–T in V4. (B) Considerable improvement after one week's rest. (C) Changes involve V1–V4 in 12-lead record. (D) Normal record after one month.

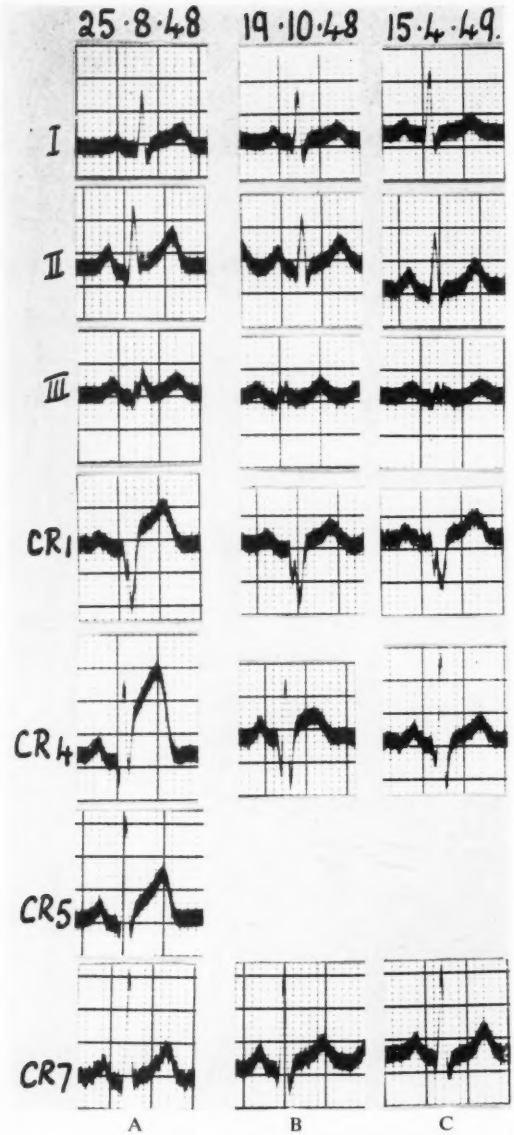

FIG. 3.—Case 3. Man, aged 42. Prolonged anginal pain 6 and 3 days previously, followed by slight pyrexia. Resumed work after 3 week's rest. No further pain. Records show acute anteroseptal ischæmia. (A) S–T elevation of 2 mm. in II, of 4 mm. in CR1, of 6 mm. in CR4, with current of injury. (B) Q wave of 4 mm. with monophasic T still seen in CR4. (C) Normal record except for W complex in CR1, 8 months later.

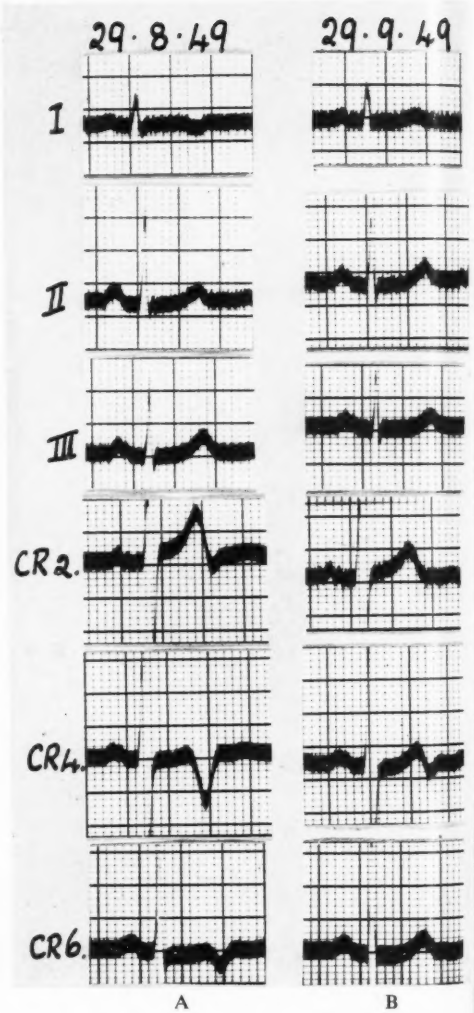

FIG. 4.—Case 4. Man, aged 62. Two months angina of effort. One week previously pain persisted after exertion for ½ hour. Rest for 3 weeks, no further angina. Records show anterolateral ischæmia. (A) Slight T inversion in I, deep T inversion in CR4 and CR6. (B) Normal record after one month.

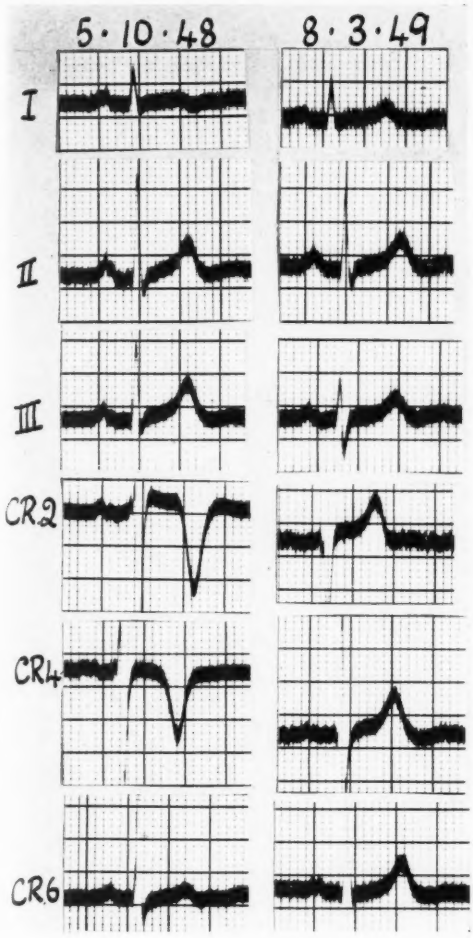

FIG. 5.—Case 5. Man, aged 49. Four months angina of effort. Coronary attack for 2 hours 5 days previously ; angina of effort worse since. Rested for 8 weeks ; still occasional angina. Records show anteroseptal ischæmia. (A) Slight T inversion in I with some coving of S–T, T inversion of 13 mm. in CR2 with S–T elevation of 2½ mm.; similar changes in CR4. (B) Normal record after 5 months.

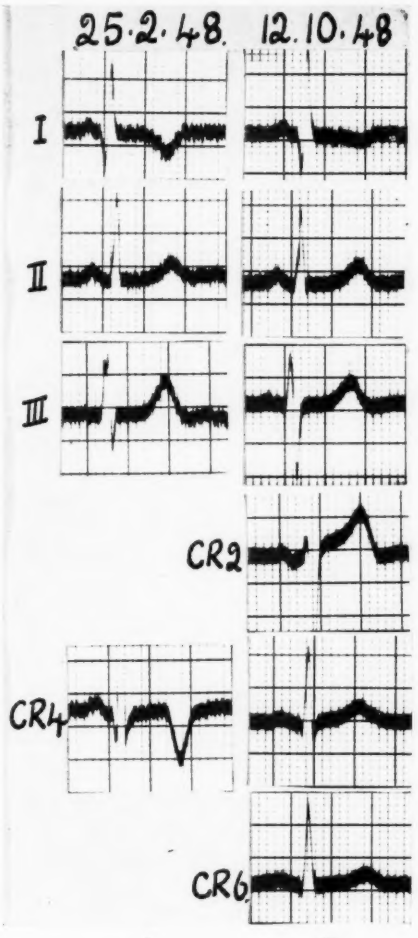

FIG. 6.—Case 6. Man, aged 47. Hypertension and occasional angina of effort. Coronary attack started while cranking cab, lasted for 36 hours. No pyrexia or fall of blood pressure. Cardiogram the same evening inconclusive. Records show antero-apical ischæmia. (A) Q wave of 5 mm. and T inversion in I with reciprocal effect in III, small Q in CR4 with T inversion of 7 mm. after 6 weeks. (B) Chest leads normal, slight T inversion and persistent Q wave in I, after 8 months.

small or absent in three records, all showing anteroseptal ischæmia ; pathological Q waves were encountered in seven instances, of these three were of anteroseptal, one of anterolateral, one of antero-apical, and two of posterior pattern. Complete restoration to normal of the electrocardiogram was seen in 14 instances (Fig 2, 4, 5, 8, 9, 10 and 11), and far reaching electrocardiographic

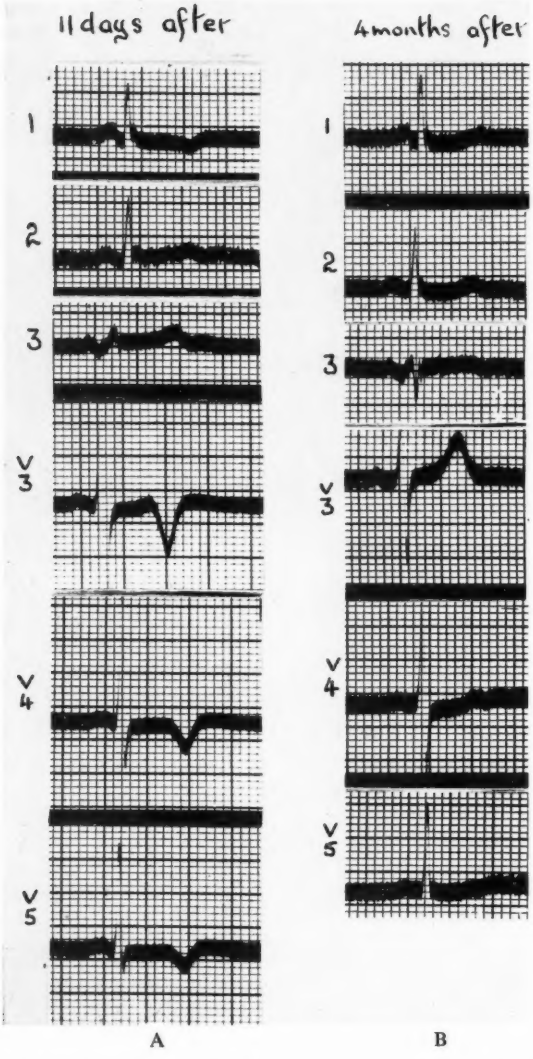

FIG. 7.—Case 7. Man, aged 71. Angina of effort for 3 months, prolonged bouts of pain 14 and 11 days previously, with vomiting and sweating, requiring morphia. No pyrexia, normal E.S.R., some fall of B.P. Resumed work after 5 weeks ; no pain for 15 months. Occasional angina of effort now. Records show anteroseptal ischæmia. (A) Changes similar to Fig 4 and 5. (B) Record restored almost to normal.

recovery in another 14 (Fig 1, 3, 6, 7 and 12). Thus, in only 6 of the 35 cases did the abnormal electrocardiogram persist, while in one patient with a posterolateral pattern subsequent changes pointed to an extension of the lesion. The increase or reappearance of a small or absent R was seen

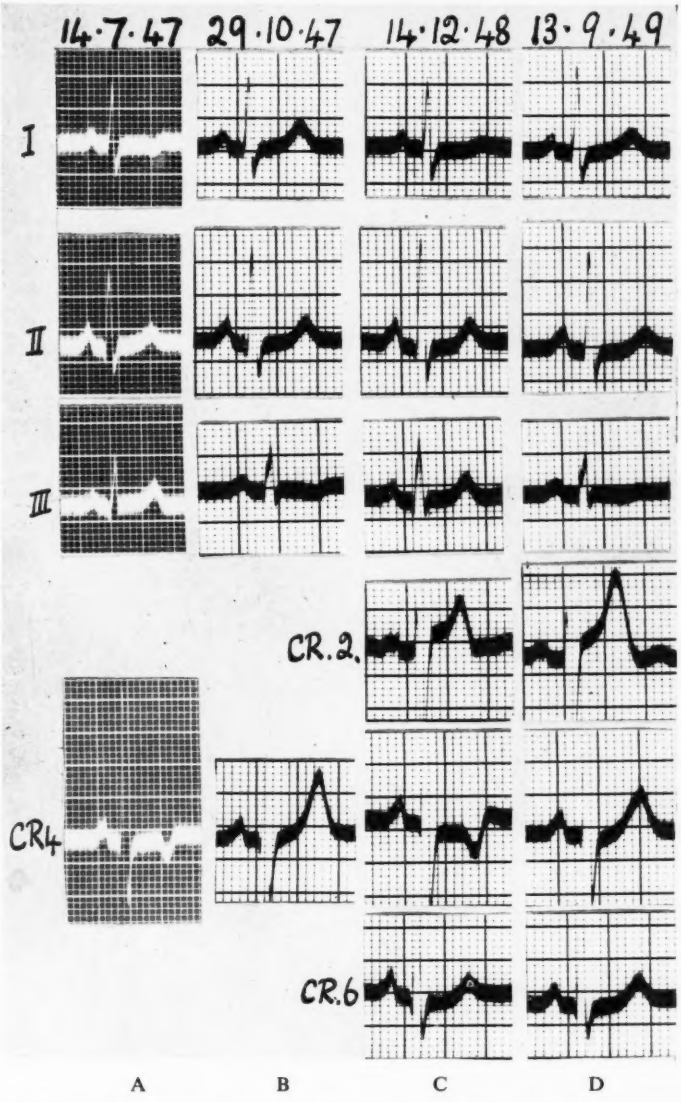

FIG. 8.—Case 8. Man, aged 48. Hypertension and angina of effort for two years. The night previously coronary attack for 1½ hours requiring morphia. Periods of frequent angina at rest and on effort during the following two years of observation. Never showed pyrexia or fall of blood pressure. Records show antero-apical ischæmia twice reverting to normal. (A) and (C) isolated inversion of T in CR4 with lesser changes in lead I. (B) and (D) normal records 3 and 9 months after (A) and (C).

three times (Fig 1 and 3) and one of these records, the only one with a current of injury, reverted almost to normal (Fig. 3). A pathological Q wave became a permanent abnormality even when other signs of myocardial injury had disappeared (Fig. 6). The time of restoration was difficult to

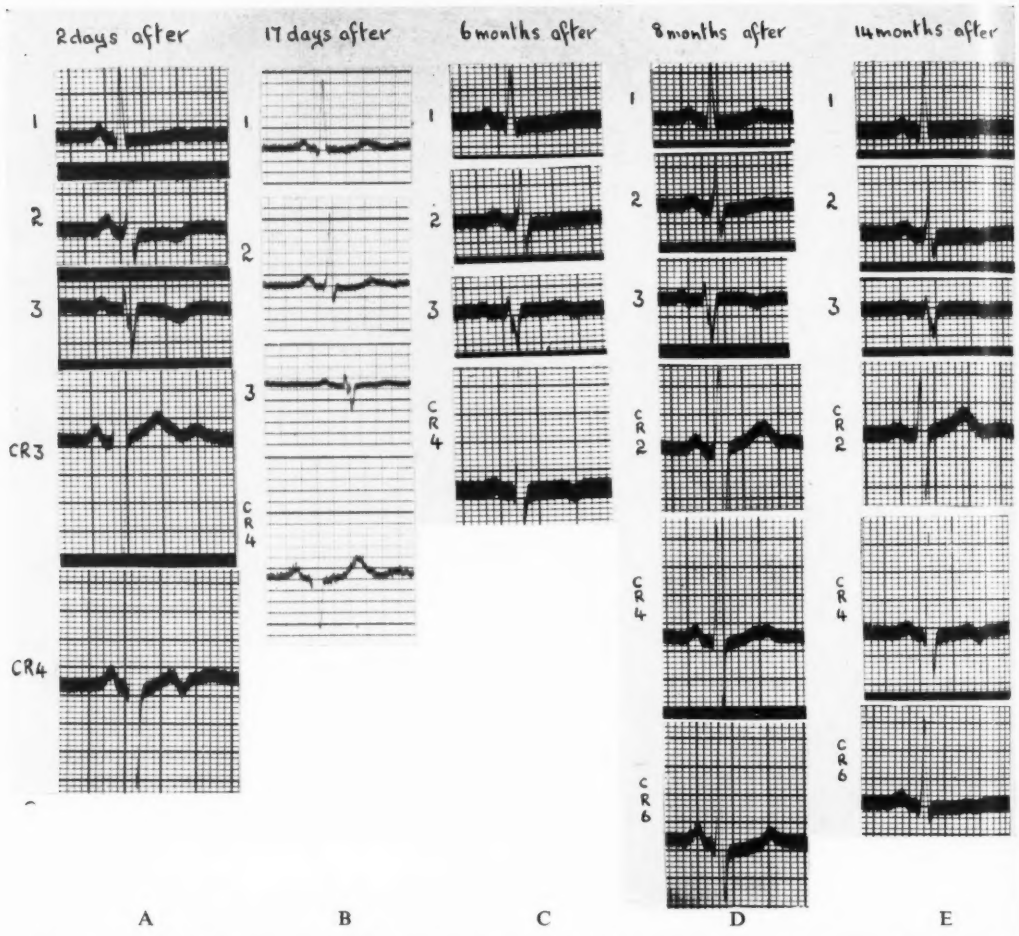

FIG. 9.—Case 9. Man, aged 57. Slight hypertension, obesity ; chain-smoker. Nov. 1947, coronary attack while dancing after heavy meal, with ectopic tachycardia and B.P. 190/135, requiring repeated injections of morphia. No pyrexia. Temporary fall of B.P. No further pain for 7 months. June 1948, frequent angina of effort and at rest. July 1948, cerebral embolus, complete recovery. Attacks now very occasional, and related to mental stress. Records show posterolateral ischæmia with intermittent reversion to normal, unrelated to clinical state. (A), (C) and (E) slight changes in all leads except CR2. (B) and (D) almost normal records.

assess, since records were taken at irregular intervals. A normal record was obtained within a fortnight in Cases 9 and 16, within three and four weeks in Cases 2 (Fig. 2) and 18 ; within five weeks in Case 4 (Fig. 4) ; within three months in Case 1 (Fig. 1), and from six months to two years in the remaining patients (Table III). The electrocardiogram of Case 9 with a posterolateral pattern varied between normal and abnormal when recorded at intervals during the following 14 months and that of Case 8 behaved similarly (Fig. 8 and 9). These changes were apparently independent of the clinical state of the patients ; normal records were sometimes obtained during periods of frequent anginal attacks and vice versa.

TABLE III

TIME OF RESTORATION OF CARDIOGRAM IN 14 CASES

Less than 2 weeks	2–5 w.	6–9 w.	10–13 w.	14–26 w.	27–36 w.	37–52 w.	More than 52 w.
2	2	1	1	3	1	2	2

FIG. 10.—Case 10. Man, aged 50. Obese. Angina of effort for two weeks ; attack never prolonged. Rest for two weeks then resumption of activity. No symptoms for 3½ years. Lately very occasional angina of effort. Records show posterior ischæmia. (A) Flat T in II, small Q and coronary T in III. (B) T upright in II, lesser changes in III. (C) and (D) Normal records 2 and nearly 4 years later.

Discussion

East and Oram (1948) out of a material of 367 cases with records diagnostic of cardiac infarction collected 28 showing a recovery of the T waves to normal. The study of the clinical history of these patients failed to give any indication suggesting the temporary nature of the electrocardiographic abnormality and the laboratory data available did not permit any conclusion regarding the severity of the attack. The prognosis in their cases was, however, good and in an average time of four years of observation—7 patients were observed for more than 8 years—only three died and one of these of septicæmia. They also emphasized the frequency of anterior ischæmia, but most of their electrocardiograms antedate serial chest lead recordings and these were only added when recovery had taken place ; therefore the location of ischæmia remained doubtful. Their Fig. 4 and 13 are both anteroseptal patterns and some of the other records showing isolated T inversion in lead IV with little abnormality in the limb leads (their Fig. 3 and 6) seem to belong to this category. Laubry and Soulié (1950) also believe that a favourable course is more likely in those cases with anterior patterns where the electrocardiographic changes are limited to a deep inversion of T in V_2 to V_6 while the ventricular complex remains normal. Myers, Klein, and Stofer (1948) in post-mortem material of 161 cases of myocardial infarction found 20 with anteroseptal infarction. In the majority of these the infarct was limited to a relatively narrow strip of the free anterior wall of the left ventricle and the contiguous anterior portion of the interventricular septum and did not extend into the lateral or posterior aspect of the left ventricle. The electrocardiographic changes in many were identical with those found in our series and consisted of conspicuous R–ST changes in V_1 to V_4 with normal QRS. In these, post-mortem examination showed small intramural and patchy subendocardial infarctions in the anteroseptal wall of the left ventricle. In the others, where QRS changes were predominant in V_1 to V_4, the infarcted zone was more extensive and at times through and through. Yet in only 4 out of 20 was anteroseptal infarction directly responsible for death ; of the remaining 16, in 12 the infarct was well healed, while in 4 it was more recent. Death ensued following a new extensive infarction in another coronary district or from such diverse conditions as cerebral hæmorrhage, bronchopneumonia, uræmia, renal abscess, intestinal obstruction, and peritonitis. Myers, Klein, and Hiratzka (1949) among their posterolateral infarctions, published two further cases with electrocardiograms similar to our anteroseptal pattern. One, in whom a posterolateral infarction coexisted, died of mesenteric thrombosis, the other of a recent posterolateral infarction. Post-mortem examination confirmed in both the existence of patchy subendocardial infarction in the anteroseptal wall of the left ventricle, recent in the first and healed in the second.

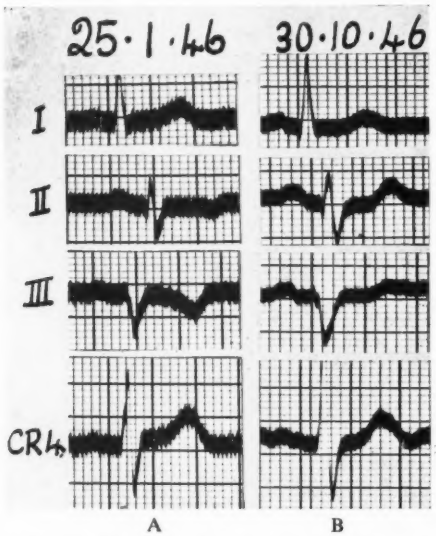

Fig. 11.—Case 11. Man, aged 60. Diabetic. Coronary attack for 1½ hours after heavy meal ; further pain one and two weeks later. Rest for 4 weeks ; No pyrexia ; W.B.C.'s normal ; slight fall of B.P. No symptoms during one year of observation. Records show posterior ischæmia. (A) Similar to Fig. 10(A). (B) Normal record 9 months later.

Myocardial recovery depends on the balance between rate of arterial narrowing and development of vascular anastomoses. Blumgart, Zoll, Freedberg, and Gilligan (1950) found only fifteen per cent of normal human hearts with interarterial communications of 40 micron diameter or more.

The septum, however, seems to be an exception. Laubry, Soulié, and Thys (1948) found septal anastomoses in 4 out of 5 healthy hearts in young people under 30, and in 16 among 29 healthy hearts in those between 40 and 70. Over 70 they tend to disappear and were found only in 4 out of 14. While in hearts without coronary disease these anastomotic channels were small, in hearts with infarcts or coronary obstruction they were almost as large as the normal perforant arteries of the septum. Thereby new circulatory conditions were created to help myocardial recovery. There

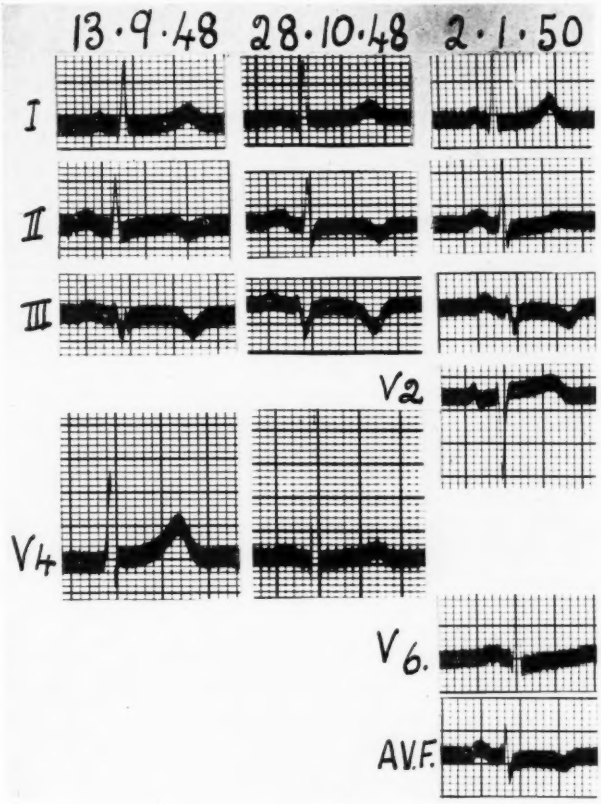

FIG. 12.—Case 12. Man, aged 73. Coronary attack 12 days previously for 2 hours ; disabling angina of effort since. Rest for a fortnight then resumed work. No pain now for 20 months. Records show posterior ischæmia. (A) Similar to Fig. 10(A) and 11(A). (B) No change 1½ months later. (C) Only partial restoration after more than one year.

is thus agreement between the French and American authors that gradually developing arteriosclerosis of the larger coronary arteries is a strong stimulus for the development of collateral circulation in the heart (Blumgart *et al*, 1950) and this applies not only to the septum but to other myocardial regions. Such a well developed anastomotic circulation may prevent myocardial infarction even in the presence of multiple coronary occlusion (Ravin and Geever, 1946). From the fact that seventeen of our series had angina before the coronary attack and a further six developed it following this, it may be presumed that in two-thirds of our series such a narrowing of the coronary arteries existed.

Treatment

There was far-reaching agreement between the clinical and the electrocardiographic features in our series, in so far as both were slight. Profound changes of the ventricular complex such as are seen in through and through infarction and endocardial involvement were absent ; thus there seemed to be no risk of mural thrombus formation. There was no shock with dangerous fall of blood pressure, and further extension of infarction therefore seemed unlikely. Consequently it was decided not to employ anticoagulant therapy but to adopt the simplest form of treatment consisting of rest in bed and sedatives. Rest in bed in 7 out of 9 patients seen in general practice was reduced to a fortnight. Although these patients were allowed to sit up in bed and to use the commode after the second day the result in these was as good as in the others who were kept in bed for from 3 to 5 weeks, and the proportion without angina after the attack even greater (Papp, 1949). This is in agreement with the results of Freedberg *et al.* (1948) in their cases with coronary failure and does not bear out the objections of Blumgart *et al.* (1950) against shortening the period of rest in bed on the ground of their experimental results. Absolute rest for these patients was regarded as not only an unnecessary hardship but as a disadvantage and they were encouraged to move in bed, to adopt the most comfortable position, to do respiratory exercises and to move the legs to avoid venous thrombosis. In addition to sedatives (phenobarbitone ½ grain, or sodium amytal 2 grains, twice daily) the following drugs were used with the aim of preventing recurring angina and with varying success : aminophyllin 3 grains thrice daily, papaverine 1½ grains thrice daily, the latter often combined with atropine sulphate 1/150 of a grain. In addition, trinitrin 1/100 of a grain was given as a routine several times a day. For the suppression of the attacks double doses of trinitrin (1/50 of a grain) were given ; if this was ineffective pethidine 100 mg. was injected intramuscularly. The effect of pethidine in these slight but often prolonged coronary attacks was better than that of morphine. It acts more quickly, has no exciting effect, and produces rapid sleep which lasts from half to one hour. Owing to the danger of addiction this drug should be used with caution.

All the patients recovered from their acute attack and were able to resume their occupations. We do not think that the cerebral thrombosis eight months after the acute attack in Case 9 or the cardiac failure in Case 15 could have been avoided by anticoagulant treatment. Extension of infarction, though not seen in our slight anteroseptal cases, was described by Rosenbaum, Wilson, and Johnston (1945), but we doubt whether these exceptions justify the use of anticoagulants in similar patients. Our Case 22 with a posterolateral pattern, the only one among 33 in whom the cardiogram showed further extension, made a good recovery and never gave the clinical impression of being seriously ill.

The period of observation of our cases is too short to be of prognostic value, but the fact that two of our patients over 70 years of age who had their acute attacks 15 and 19 months ago are well and active, justifies an optimistic outlook. Although we have not experienced them, fatalities may occur in slight coronary attacks (East and Oram, 1948) presumably through ventricular fibrillation (ectopic tachycardia was seen during the attack twice in our series). The risk of further severe attacks after months or years is as real in slight as in extensive myocardial infarction, but this cannot be prevented by any available treatment during the acute attack.

Summary

Out of a material of 109 consecutive cases diagnosed as cardiac infarction, comprising hospital in-patients, patients seen in consultant and in general practice, 33 (little less than one-third) had slight coronary attacks. Shock and cardiac failure were not found in them, the blood pressure never fell to dangerous levels, clinical and laboratory signs of myocardial necrosis were slight or absent, and all the patients made uncomplicated recoveries. The ages of these patients varied between 42 and 73, two being over 70. The proportion of men to women was three to one.

Electrocardiograms recorded in 35 attacks (two patients had two attacks and both slight) showed the following patterns of myocardial ischæmia : anteroseptal 17, anterolateral 7, anteroa-pical 2, posterior 6, posterolateral 3. Changes in S–T and T patterns were prominent in all ; diminution or absence of R was encountered in 3 and pathological Q waves in 7 instances. Complete restoration to normal or far reaching electrocardiographic recovery was almost the rule and resulted in 28 instances. Anteroseptal patterns showed the greatest rate of restoration and 16 out of 17 became normal or nearly so, and so did 5 out of 7 anterolateral, and 5 out of 6 posterior patterns. Recovery took place within two months in 5 patients and from 4 to 16 months in the remaining 23. In 6, the electrocardiogram remained unchanged and only one posterolateral pattern showed further extension of infarction.

These electrocardiographic patterns are suggestive of small intramural or patchy subepicardial infarctions and as such they are in close agreement with the slight clinical symptoms. The notable frequency of cardiographic restoration suggests good collateral circulation in the infarcted areas, stimulated perhaps by pre-existent arterial narrowing (more than half of these patients had long standing angina and two-thirds continued having it after the infarction).

Anticoagulant treatment is not indicated since the risk of thrombo-embolic complications or extension of infarction is so slight. Further thrombosis in major coronary branches must remain an ever existing danger.

We are indebted to the Physicians of the Charing Cross Hospital for permission to use certain of their cases, and to Miss Anne Smith, cardiographic technician to the hospital, for electrocardiography of many cases and for the mounting.

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TUBEROUS XANTHOMATOSIS

BY

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Tuberous xanthomatosis is a rare condition, with dominant inheritance, but it is possible that its victims, who commonly show visceral and particularly cardiac atheroma, possess in homozygous form one or more genes that are fairly widely distributed and expressed, when heterozygous, as hypercholesteræmia and coronary atheroma without xanthomatosis (Bloom, Kaufman, and Stevens, 1947). The importance of the condition may therefore be out of proportion to the rarity of its occurrence, and this possibility is one reason for recording the history of a family in which it occurs. A second reason is the development in one of the child victims of the disease of intermittent claudication and the Stokes-Adams syndrome.

History of the family

Mrs. M., a widow of 46 years, with two surviving children, was first examined in November, 1938, when my opinion was sought for attacks of vomiting and abdominal pain which had been recurring at intervals of a few weeks for some years. The menopause had occurred in September, 1938. She was a stout woman (height 66 in., weight 196 lb.) with pronounced xanthelasma of the eyelids which she reported to have been present in her mother also: she had no other xanthomatous lesion. There was a moderate hypertension (170/110). Her pain suggested gall bladder disease but the cholecystogram was normal. The blood cholesterol was 137 mg. per 100 ml. She had never been jaundiced.

She was not seen again until 1940, when she was admitted to hospital with acute bronchitis. She was orthopnœic and complained of severe substernal pain: the blood pressure had fallen to 70/50 but rose after a few days to 110/75. Her cardiogram showed left axis deviation, with some slurring but no definite deviation of S–T, and no T inversion (leads I, II, III, IVR). The P–R interval was 0·22 sec.; Q–T, 0·36; and the rate, 96. She made a good recovery from this attack, and had no further symptoms of coronary disease: her cardiogram was repeated in 1944, and showed the same features.

Her husband had died suddenly in 1935, at the age of 42, after bathing; he had been a keen football player, but gave up the game at the time when he also changed from manual to sedentary work: as a result, he bacame stout. Her brother had lost two children in separate bathing accidents.

Mrs. M. had three children. The first (Case 1), died suddenly at the age of 12. I am indebted to Drs. Ian MacLeod and J. H. Kirkpatrick for the following information about Case 1, and the remaining children (Cases 2 and 3) were examined by me in 1942.

Case 1. M. M. until her twelfth year had seemed a healthy child, but had become rather fat, and for some years her mother had noticed nodules over the tendons at the ankle: they were not painful. At the age of twelve she had an attack characterized by sudden loss of consciousness, cyanosis, deep sighing respiration, and incontinence of urine: there was no clonic or tonic spasm of the limbs or face.

She made a quick recovery from the attack and had no residual symptoms. A second attack followed after a few days; there was no obvious association with exertion. When examined, she was found to have xanthomatous nodules on the legs, and patches of xanthoma on the face and buttocks. Her blood cholesterol was found to be more than 300 mg. per 100 ml. a few days before her third attack, which was fatal.

This child died at home, but a necropsy was performed by Dr. Kirkpatrick, and showed the lumina of the coronary arteries reduced to pin-point size from diffuse atheroma, which was also present in the aorta. There was no definite cardiac infarct. The trachea was studded with small xanthomatous nodules.

Case 2. A.M., the elder boy, was thirteen. Weight, 86 lb.; height, 56 in. He was freckled, but no xanthomatous lesions were seen. Physical examination was negative and the cardiogram normal (P–R, 0·16 sec.; QRS, 0·08; Q–T, 0·28, and rate 108). His blood cholesterol was 342 mg. per 100 ml. He was re-examined in 1944, when his blood cholesterol was 220 mg. per 100 ml.: the cardiogram was again normal and no abnormal physical signs were found.

Case 3. J.M., the younger boy, was twelve. He also was freckled and rather plump (height 54 in.; weight 72 lb.) He had no xanthomatous lesions, but a yellowish hairy nævus on the forearm. Physical examination was negative. His blood cholesterol was 322 mg. per 100 ml. His cardiogram (standard leads only) showed sinus rhythm, normal axis, P–R 0·18, QRS 0·08, Q–T 0·4 sec., rate 72, and a biphasic T in leads I and II.

The following year (1943) I was called to see him because of attacks of syncope. He had complained for some months of tingling in the feet and pain in the calves when running, and of weakness in the legs that sometimes made him stumble. Shortly before I saw him, he lost consciousness when he was on his way home from school, but recovered after a few minutes. The following afternoon he had a " spasm " of the hands and feet which his doctor thought not unlike tetany, and again lost consciousness for some minutes: a similar attack occurred later in the day. Two days later, the spasm was repeated, but without loss of consciousness, lasting about five minutes. For the next week he seemed well, but one morning complained of headache on waking: after dressing he went out, but immediately afterwards had a generalized epileptic fit lasting ten minutes. He was examined later the same day and admitted to hospital.

On re-examination (1943) he was symptomless. The heart was regular, the sounds normal, and there were no murmurs. Blood pressure, 110/80. Pulsation could be easily felt in both arteries of the feet. No abnormal signs were found in the nervous system, and an X-Ray of the chest was normal. Blood cholesterol, 322, calcium 9·4, sodium 320, potassium 20 mg. per 100 ml. During his two weeks' stay in hospital, he felt quite well and had none of his previous symptoms. Arterial biopsy was performed by Mr. A. J. Hamilton, and photomicrographs of sections taken from this specimen are reproduced in the figure. I am indebted to Dr. H. J. Kirkpatrick, pathologist to the Royal Northern Infirmary, Inverness, for the following reports of sections, the first being stained with hæmatoxylin-eosin.

" *The Media.* The muscle fibres are separated by fine collagen fibrils and by deposits of globules, probably of lipoid. Many of the muscle fibres show degenerative changes: some are atrophic, others are swollen and stain poorly, and in a few the muscle substance is largely replaced by fatty material.

" *The Intima.* There is patchy thickening of the intima due to increase in fibrous tissue and fat deposits. The fibrous tissue is undergoing degeneration, and in the thicker parts it has a granular, rather amorphous appearance. The endothelium is for the most part intact but an occasional endothelial cell is distended by fat.

" *The Adventitia.* The adventitia is moderately thickened and there is occasional deposit of fatty material close to the media.

" *Sections stained with Verheoff-Van Giesen.* The internal elastic lamina forms a single layer and is complete; in one or two places the lamina shows commencing degeneration. There is no stainable elastic tissue in the media. There is no apparent abnormality of the elastic tissue of the adventitia.

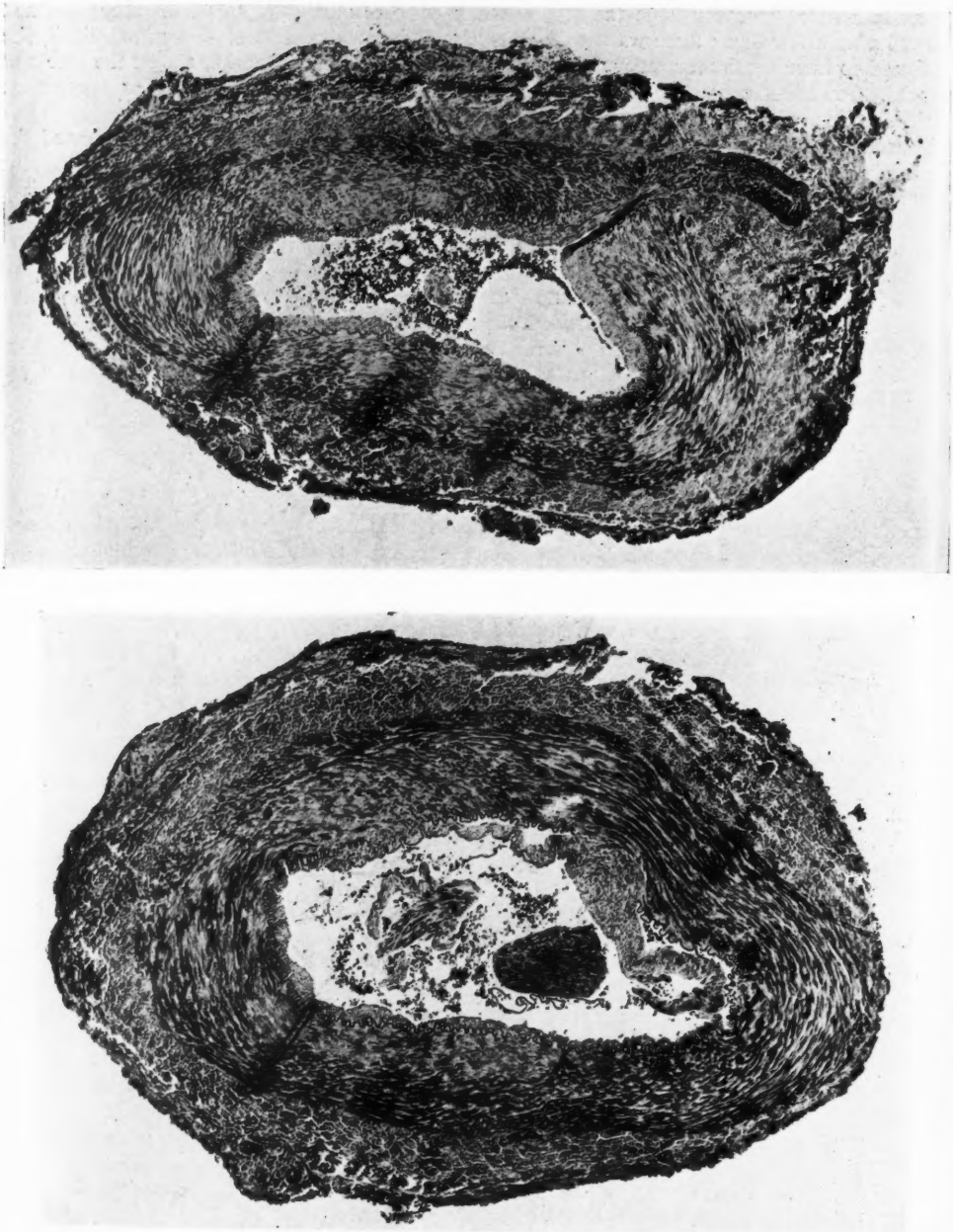

FIG. 1.—Photomicrographs of biopsy specimen from artery of medium calibre from Case 3, aged 13. (× 50). The intima is irregularly thickened; muscle fibres of the media are separated by lipoid, also present within the fibres and in the intima. Connective tissue is increased in the media and is the site of fatty degeneration.

"There was not enough tissue for frozen sections for fat stains and examination by polarized light, but I think it fairly clear that the deposit in the vessel wall is of lipoid or fatty material."

Subsequent Progress. During the following year he was seen from time to time and remained symptomless except for discomfort in his legs when active. His blood cholesterol remained high, and was not influenced by low-fat diet or by thyroid extract 3 grains daily. The following figures were obtained, the lowest bearing no clear relation to thyroid treatment; 294, 332, 192, 256, 270, 332, 268, 228, 272, 348 mg. per 100 ml. In 1945 he was readmitted to hospital after a prolonged epileptic attack: mental dulling was evident, but slowly improved. There were no residual signs to suggest a focal origin. No evidence of xanthomatosis had appeared. This boy was last seen in 1946, apparently well, and is now (1949) reported as symptomless and working as a van driver. Since 1945 he has taken each day 1·5 grains of thyroid extract and 1·5 grains of phenobarbitone. The important features of this boy's cardiograms are shown below. In October, 1943, the only abnormal symptom or sign was the high blood cholesterol: his 1942 cardiogram is normal except for the biphasic T. In 1943, after his first syncopal attack, TIV is inverted, but the most remarkable feature is the duration of Q–T, which is almost 0·5 second, with a heart rate of 90. Thereafter his Q–T interval is always prolonged. TIV reverts to upright until the 1947 record, taken at a time when I was no longer in touch with him: the Q–T in this record is 0·45 seconds, with a heart rate of 90. S–T shows no significant deviation throughout the records.

Date	Rate	P–R	QRS	Q–T	TI	TII	TIII	TIV	
October 1942	75	0·18	0·07	0·36	↕	↕	↔	—	
December 1943	90	0·16	0·08	0·50	↑	↑	↓	↓	
January 1947	90	0·17	0·07	0·46	↑	↑	↓	↑	
,, ,, ...	90	0·16	0·08	0·40				↑	Before exercise
,, ,, ...	90	0·16	0·08	0·40				↑	After exercise
February 1944	90	0·16	0·08	0·42					Before and after exercise
August 1944	105	0·16	0·08	0·40	↑	↑	↓	↑	
January 1945	105	0·16	0·08	0·40	↔	↑	↓	—	
January 1946	100	0·16	0·08	0·44	↑	↑	↔	↑	
February 1947	90	0·18	0·08	0·45	↕	↕	↔	↓	

Comment

Increase of the blood cholesterol occurs in such a variety of clinical syndromes that it has, as an isolated phenomenon, little value in diagnosis. Xanthosis is uncommon and distinctive. A familial tendency to atheroma and death from coronary disease is well recognized and represents one of the most important obstacles to longevity. High levels of the blood cholesterol in these cases are common, possibly invariable. I have records of several such families, of which the following is an example:

E.L., a postman, aged 40, developed angina when on active service, six months before I saw him in 1942, and was discharged from the army. His two sisters had died young, at ages 13 and 36. Two of his brothers had died suddenly, at ages 40 and 42. He was an anxious man, fully conscious of the significance of his family history, and rather obese. No xanthomatous lesions were seen. His cardiogram, which had shown T inversion in one army hospital, was normal except for left axis deviation, but exercise produced some S–T deviation. His B.M.R. was normal. The blood cholesterol ranged from 210 to 280 mg. per 100 ml., but a few months later was 420 mg. In 1945 he collapsed and died while out walking. This man's surviving brother, aged 35, weighed 200 lb. Physical examination showed a broad aorta; his blood cholesterol was 236 mg. per 100 ml.

Coronary disease is rare in childhood. Extreme and unexplained calcification of the arteries may occur, even in infancy (Leys, 1950*b*). In later childhood the syndrome of lipoidosis is a possible cause. Unexplained sudden death in later childhood, especially when there is more than one victim in the family, suggests this syndrome, and sudden death suggestive of cardiac

disease below the age of 40 demands a study of sibs and particularly of the children. The frequency of coronary obstruction as a cause of death is increasing and the age incidence decreasing. Occupational analysis suggests strain and hypertensive disease as main causes (Ryle and Russell, 1949), but any observation that tends to explain the mechanism of the atheromatous process must be of value.

The influence of diet in the genesis of lipoidosis and the relationship of increase in the blood fat to atheroma is undecided. This problem is briefly discussed and references given in my paper on the inheritance of a factor causing sudden death in adolescence (Leys, 1950*a*). The attempt to reduce the level of the blood cholesterol by thyroid treatment is logical in view of the accumulation of cholesterol in atheromatous lesions; although no good evidence was obtained of such a therapeutic effect in this case, it is suggestive, in view of his sister's story, that thyroid effected a diminution of tissue cholesterol in Case 3. The long Q–T in this boy is a distinctive finding and may well be a feature of such cases: it was not prolonged in either his mother or his brother.

Summary

A family is reported in which xanthelasma appeared in two generations and, in the third, tuberous xanthomatosis leading to death from coronary disease of the eldest child at the age of 12, and arterial claudication and the Stokes-Adams syndrome in the second, at the same age. Both these children, and the remaining boy showed hypercholesteræmia. It is suggested that the father of these children, who died suddenly at the age of 42, may have been heterozygous for the gene and the children homozygous.

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THE AGEING OF CARDIAC INFARCTS, AND ITS INFLUENCE ON CARDIAC RUPTURE

BY

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In about 9 per cent of necropsies upon cases of fatal recent cardiac infarction hæmopericardium is found as a complication (Edmondson and Hoxie, 1942; Diaz-Rivera and Miller, 1948; Friedman and White, 1944). Rupture of the heart is practically confined to the first three weeks after infarction although it occasionally occurs at later stages with cardiac aneurysm. Death is not usually immediate upon rupture, but follows at an interval of several hours, being probably due to circulatory failure caused by cardiac tamponade. Rupture occurs less frequently when cardiac infarction has been recognized, and the patient is at rest in hospital; more often, and in at least five of our nine cases, the catastrophe has occurred in an imperfectly treated patient arriving at hospital either moribund or dead. In this connection it is of interest that Jetter and White (1944) found that rupture of recent cardiac infarcts occurred in no fewer than 73 per cent of a small series (27) of patients in mental institutions; they had made no complaint of pain and therefore had not been treated. In the absence of clinical evidence the authors estimated the age of the infarcts by the histological criteria of Mallory *et al.* (1939). Such criteria may thus assume medico-legal importance in the absence of a clear history of the onset of infarction, since microscopical examination may be the only method of estimating the age of the lesion.

The purpose of this report is to re-examine the sequence of histological changes in the myocardium in recent infarction, and to estimate accordingly the period at which hæmopericardium is likely to supervene.

From a total of 216 cases of recent infarction that came to necropsy in this Institute a series of 18 cases uncomplicated by rupture was selected on the strength of a clear history of the onset being available, together with adequate histological preparations. The cases provided material dating from one day onwards, with the exception of the third day, when no representative sections were available. The results of this study were then compared with those of Mallory *et al.* (1939).

Nineteen of the 216 cases (8·8%) were complicated by hæmopericardium. Of these 10 were discarded on account either of the inadequacy of the histological preparations, or from the presence of some complicating factor such as syphilitic aortitis or polyarteritis nodosa. The period at which rupture occurred was estimated, in the remainder, on the basis of the histological criteria acquired from study of the uncomplicated 18 cases.

Stages of Healing of Cardiac Infarcts

Macroscopic appearances. About 15 hours after coronary thrombosis the infarct is usually pale, swollen and œdematous. This appearance becomes more marked until, at about 36 hours, it begins to acquire a hæmorrhagic border. The central part of such an infarct appears obviously dead, being opaque and yellowish or yellowish-grey.

On succeeding days the clarity of definition of the infarct increases; by about the middle of the first week its centre is of rubbery consistency and the hæmorrhagic border is most distinct, although

not always present. Towards the end of the first week the infarct sometimes appears slightly shrunken; the area of central necrosis may become softened and grey. Irregularity of the infarct, or of the plane of section, may give an appearance of mottling with red, rather than distinct zones of grey and red. Obvious thinning of the infarcted myocardium occurs after about three weeks.

Before scarring becomes evident at 6 to 8 weeks, the infarct often appears brownish. By three months the tissue on section is white and firm, although vascularized granulation tissue is still recognizable. Tough white fibrous tissue is the final product of a healed infarct.

Microscopical appearance. The character of the cellular exudate is the most valuable feature in estimating the age of a young infarct and data about the time these changes are found are shown in Fig. 1.

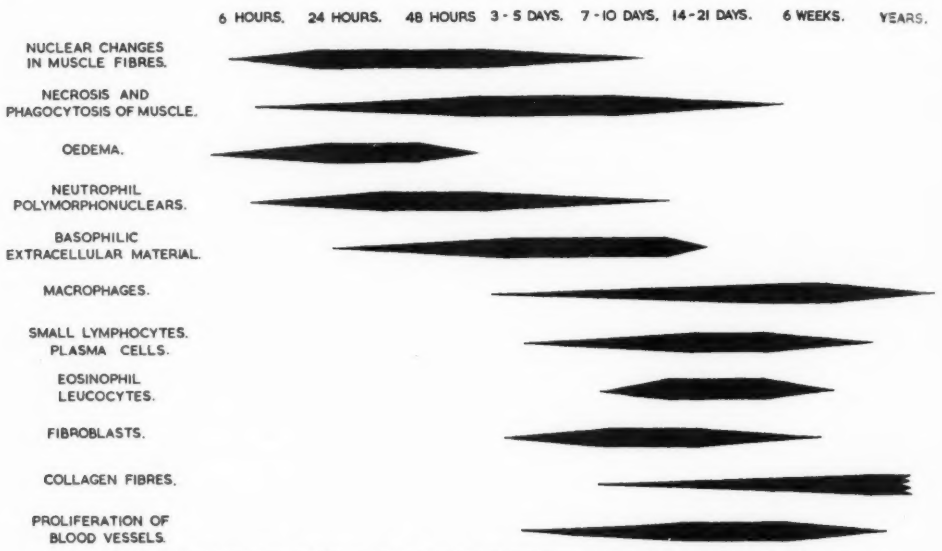

FIG. 1 The character of the cellular exudate at various stages after cardiac infarction.

Neutrophil polymorphonuclear leucocytes are the typical cells of the earliest stages. They appear at about six hours after cardiac infarction, increase in number rapidly after 24 hours, and at 48 hours are massed on the periphery of the infarcted area, penetrating between the dead muscle fasciculi for a short distance (Fig. 2). These cells are most numerous from the third to the fifth days. At 48 hours necrotic changes appear in individual leucocytes. Pyknotic nuclear remnants become increasingly abundant at successive stages, and an extracellular basophilic material, probably derived from the disrupted leucocytes, appears in increasing quantities around the necrotic muscle. This, combined with œdema—one of the earliest features—separates the muscle fasciculi, alive or dead. The basophilic material is most prominent between the fourth and tenth days and with the cellular leucocytic debris has disappeared towards the end of the second week, although sometimes persisting centrally within a large infarct for longer periods.

By the fourth day *large mononuclear macrophages* are present in places at the outer borders of the infarct, peripheral to the degenerating leucocytes. They increase to a maximum at the end of the sixth week, subsequently declining gradually, although present for as long as two or more years. These macrophages phagocytose fragments of the necrotic muscle, ingest pigment from the destroyed muscle cells, and become swollen, golden-yellow and granular. This pigment is present within the macrophages by the ninth day. Others appear foamy.

Small lymphocytes appear at the periphery of the infarct at the fourth day but are scanty; they are present in greater numbers, and accompanied by plasma cells, at about the seventh day and increase to a maximum towards the end of three weeks; they then diminish in number, although they may persist after many months.

A few *eosinophil leucocytes* appear at the seventh to eighth day and increase rapidly in number

FIG. 2.—Border of infarct at 40 hours showing zone of neutrophil leucocytes; necrotic muscle above. Hæmatoxylin and eosin. Magnification, × 103.

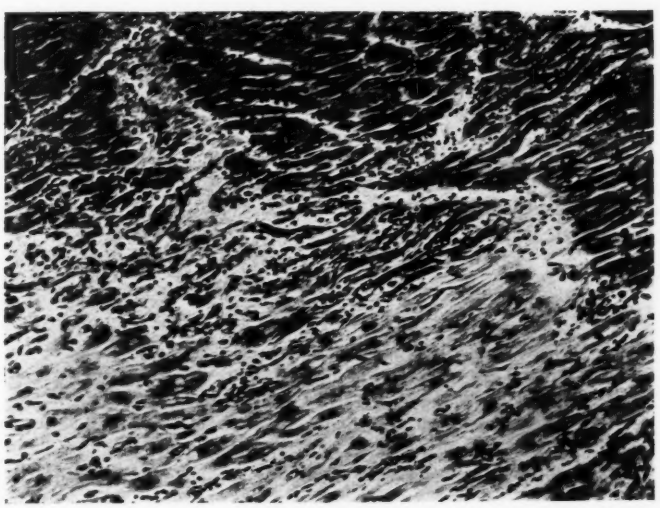

FIG. 3.—Border of infarct at 4 days showing young granulation tissue; necrotic muscle above. Hæmatoxylin and eosin. Magnification, × 95.

till about the twelfth day. When abundant they are characteristic of the third week, and are usually much fewer by the beginning of the fourth. They are not, however, a reliable indication of the age of an infarct since they may appear earlier or persist longer than the times mentioned, and may indeed be absent when their presence is most expected.

Fibroblasts are present in places by the fourth day, proliferating around the periphery of the infarcted muscle. They appear first, as part of a young granulation tissue, where the infarct approaches the endocardium or pericardium (Fig 3). At an early stage their cytoplasm is basophilic, but later this characteristic is lost. Collagen fibrils appear first about the ninth day, and the spindle fibroblasts, numerous at this period (Fig. 4), later become fewer and smaller; their nuclei

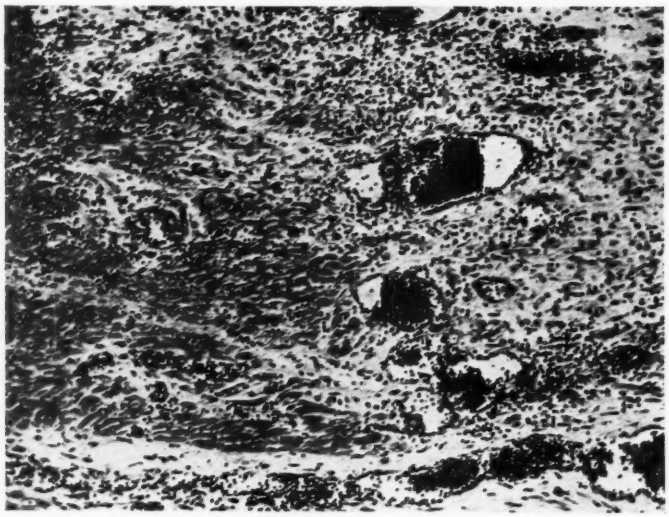

FIG. 4.—Organizing granulation tissue, rich in spindle fibroblasts and dilated capillaries, invading border of infarct at 10 days. Hæmatoxylin and eosin. Magnification, ×97.

become smaller and more elongated after the third or fourth week. In the early stage of healing these cells are arranged irregularly, but after from two to three weeks their long axes become arranged parallel to the adjacent muscle fibres and visceral pericardium (Fig. 5).

Proliferating capillaries sprout into the infarct from its periphery and often give rise to small extravasations of red corpuscles. Thin-walled, and at first closely packed, they appear in the middle of the first week, the earliest indications of proliferation being present on the fourth day (Fig. 3). These new vessels are most abundant from 3 to 6 weeks, and later become less numerous.

In the *cardiac muscle* the earliest sign of cellular degeneration is found in the nuclei, some of which become swollen and pale with a crenated nuclear membrane. This appearance was noted at 5 hours. Later the nuclei become fragmented and disappear by karyolysis; others undergo pyknosis. At about 6 to 12 hours after coronary thrombosis, the cytoplasm becomes " glassy," and the striations less prominent, although these may persist indefinitely. The cytoplasm appears increasingly hyaline and eosinophilous from coagulation necrosis and this, though often patchy, is most marked at about four to six days after thrombosis.

Phagocytosis of muscle-fibres by macrophages produces a clearly cut edge to the mass of necrotic muscle after about two weeks, but although the process continues steadily, necrotic muscle may persist for many months in a large infarct.

The results of microscopical examination have been presented in Fig. 1.

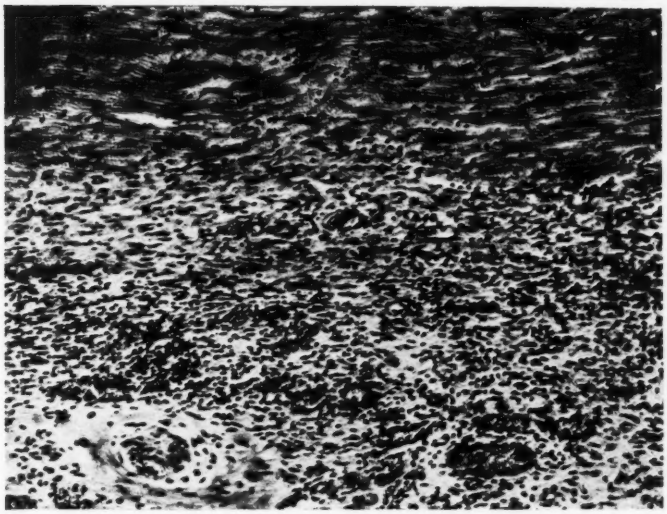

FIG. 5.—Border of infarct at 15 days showing cellular granulation tissue with many spindle fibroblasts parallel with necrosed muscle fibres. Hæmatoxylin and eosin. Magnification, ×105.

THE RUPTURED INFARCT

Macroscopic appearances. In almost every case the infarct was described as pale, anæmic or yellowish, words that placed its probable age at 5 to 21 days. One described as " firm, opaque, pale and yellowish " was known from the clinical history to be not more than three and a half days old. In none of the cases of hæmopericardium had rupture occurred sufficiently long before death for organization of the pericardial clot to be distinguished at necropsy.

Microscopic appearances. Sections, in all these cases, included enough of the edge of the infarct to enable its age to be assessed in terms used in the larger series. In most cases blood had infiltrated in some degree between the fasciculi of the necrotic muscle surrounding the site of rupture, without obscuring the peripheral zone.

The age, estimated in this way, varied from about 10 to 14 days at the oldest, to about 24 hours at the earliest. On histological grounds, the age of nine ruptured infarcts was estimated as follows: one of 1 day, two of 3½ to 5 days, two of 6 to 7 days, one of 7 to 8 days, two of 9 to 10 days, and one of 10 to 14 days.

Of these 9 cases, 5 had a clear clinical indication of the age of the infarct which agreed with the assessment made on histological examination.

DISCUSSION

These observations on the stages of healing of infarcts and on their time-relationships agree with those of Mallory *et al.* (loc. cit.) except in a few details. Thus, no particular emphasis should be laid on the basophilia of fibroblasts which they regard as an important feature, because such a feature is common to rapidly proliferating cells. Again, for reasons that are given above, the appearance and development in conspicuous numbers of eosinophil leucocytes in the infiltration is an unreliable criterion of the age of an infarct. On the other hand, the orientation of fibroblasts is sometimes helpful for such assessment. The earliest changes found are intercellular and intracellular œdema of the muscle-fibres, and their nuclear changes.

The close agreement, in general, between my findings and those of Mallory and his co-workers suggests that infarcts of less than one week can be accurately dated to within 24 hours; in the second week, to within 36 to 48 hours, and up to 6 weeks old, within about 7 days. The corollary to this, namely the period during which rupture is likely to complicate infarction, is obviously of the greatest importance. Few attempts have been made to assess this.

Isolated examples of hæmopericardium have been recorded since the first description by William Harvey but the first pathological analysis is that of Krumbhaar and Crowell in 1925. They described 22 cases of spontaneous rupture and collected a further 632 that had been reported. Though histological examinations were made in most of their cases, the changes were not precisely related to the age of the infarct. In their monograph on the clinical features of coronary thrombosis Levine and Brown (1928) review 46 necropsies including 9 cases of hæmopericardium. These authors were the first to cite histological changes as an index of the age of the lesion, but their observations were general in character. They concluded that necrosis predominates from the fourth day to the end of the third week, that repair by collagen can be demonstrated on the sixth to seventh day but is not striking till the third week, that cicatrization sufficient to prevent rupture may be present by five weeks, and that firm scar-tissue may be observed eight weeks after the onset.

In the series of Mallory *et al.* (1939) there were eight examples of cardiac rupture. They calculated that this usually occurred within the first ten days of infarction. Adding their cases to those of Levine and Brown they estimated that 65 per cent ruptured in the first week, 29 per cent in the second week, and more rarely at later stages. Analysis of the present series is in agreement with this conclusion.

Conclusions

The age of a cardiac infarct can be told from its histological appearances, with an accuracy within a range of 24 hours during the first week and of wider range at later stages.

The sequence of histological changes in the material examined agreed in general with that described by Mallory, White, and Salcedo-Salgar (1939).

Using the criteria described, the age of the infarct was estimated in nine cases of hæmopericardium. The ages ranged from 1 to 14 days, and in seven cases it was between 3½ and 10 days. In five cases the clinical history agreed with the ages assigned on histological grounds.

It is a pleasure to express my thanks to Professor Dorothy Russell for help in the preparation of this paper.

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CLINICAL MEASUREMENT OF THE ELECTRICAL RESISTANCE OF A PATIENT WITH AN AMPLIFIER TYPE OF ELECTRO-CARDIOGRAPH

BY

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The electrical resistance of the patient plays an important part in the procedures for recording the various unipolar limb leads. As ascertained in a previous study (Jeanneret, 1949), the relationship between the amplitude of unipolar limb lead electrocardiograms and the skin resistance depends on potential losses through the shunts existing in certain circuits.* The resistance of a biological electric current generator is an important factor for all procedures where it has to support a load (Kahlson, 1920; Holzer, 1936), as is the case for the galvanometric method, as well as for the electronic amplifiers when a shunt exists in the patient circuit.

In the present paper we merely intend to describe the method that served us for quick clinical measurements of the body-and-electrode resistance with an ordinary amplifier electrocardiograph. Thus it was also easy to verify clinically a new process for lowering the patient's skin resistance, as described by Bell *et al.* (1939), and to prove that this process entirely meets the requirements of the unipolar limb leads (Jeanneret, 1949).

Thirty years ago, Einthoven (1916), followed by Burger (1926), measured the body resistance with a string galvanometer. This is shown in Fig. 2. Tracing K shows the response of the string to the standardizing signal, without a patient in the circuit and tracing L the response with a patient in series. Knowing the string resistance, it is easy to calculate the body resistance. Unfortunately the results of this method may be distorted by the electrical capacity of the skin; furthermore the string instrument is seldom used in the hospitals on the Continent. For these reasons, it proved necessary to find another clinical method; the laboratory procedures for determining the d.c. resistance and the a.c. impedance of the human body have not been overlooked, but they require special equipment and their accuracy is greater than needed for our purpose (Einthoven *et al.*, 1922; Holzer, 1936; Bell *et al.*, 1939; Schaefer, 1942; Wyss, 1946).

Principle of the Method

If a source of electromotive force " e " and internal resistance " r " is connected across the terminals of a resistance " s ", then a potential difference given by the expression

$$v = e \times \frac{s}{s+r} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

will be developed between these terminals. The potential drop (e−v) may be expressed as a percentage of " e " and this value called " Y ". Thus:

$$Y = \frac{100(e-v)}{e} \text{ per cent} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Combining equations (1) and (2):

$$Y = \frac{100r}{s+r} \text{ per cent} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

* For example, in the circuit as described originally by Wilson (1934).

This expresses as a percentage the drop between the open-circuit voltage " e " and the potential difference " v " at the terminals of a source connected across a resistance. Finally equation (3) gives:

$$s=\frac{100r}{Y}-r\Omega \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

It is easy to record with an ordinary high input-impedance amplifier cardiograph the open-circuit voltage (" e ") of a source of known internal resistance and then to record its voltage " v " connected across the human body (" s "). From the deflection produced by " e " and " v ", " Y " may be readily found (equation 2) and the resistance of the patient's body can be calculated from equation (4).

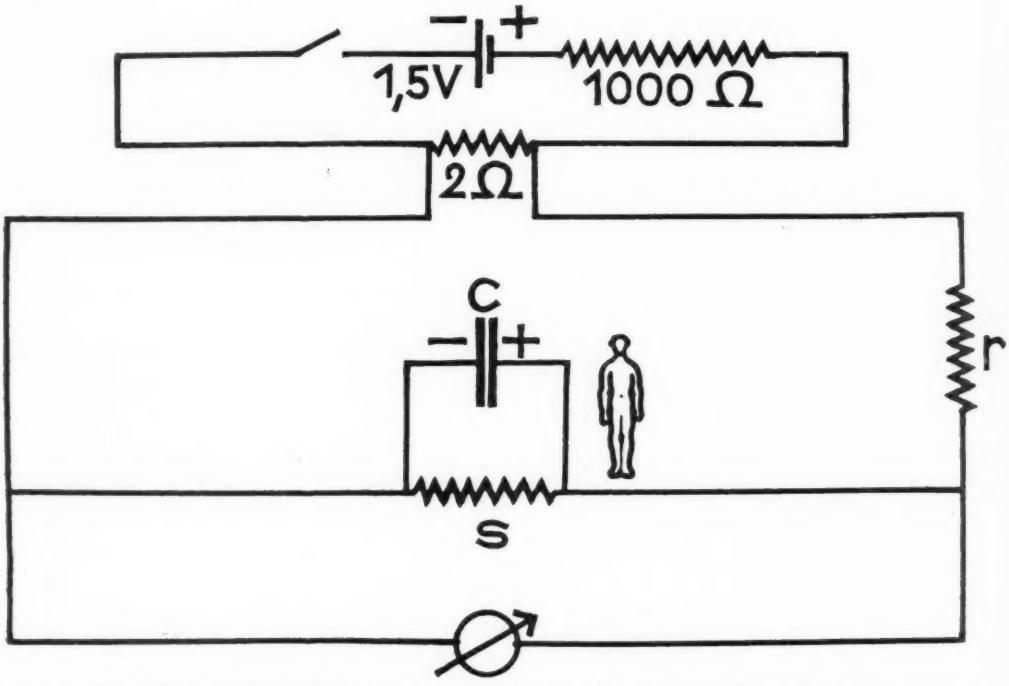

FIG. 1.—Circuit for measuring the body resistance, used in conjunction with an amplifier cardiograph, by connecting a potential difference across the patient. The source of current consists of a voltage divider (top) in series with a dry cell of 1·5 V providing about 3 mV at the terminals of the 2Ω resistor. A switch supplies rectangular potential waves. The resistor " r " plays the part of the internal resistance of the source. In order to test the effect of skin capacity the potentials are connected across a resistor in parallel with a condenser (C). Further details in the text.

THE APPARATUS

The open-circuit voltage (Fig. 2 A) generated by a voltage divider (Fig. 1) is registered through the total resistance (r+2Ω), then it is recorded when shunted across the patient (Fig. 2 B). By measuring from each tracing the deflections thus obtained, the value " Y " is readily calculated (equation 2) and " s " can be found (equation 2).

The resistance (r+2Ω) of Fig. 1 plays the part of the internal resistance of the source and must be introduced in equation (4). As " r " is great with regard to the 2Ω resistor of the potential divider, " r " may be substituted for (r+2Ω).

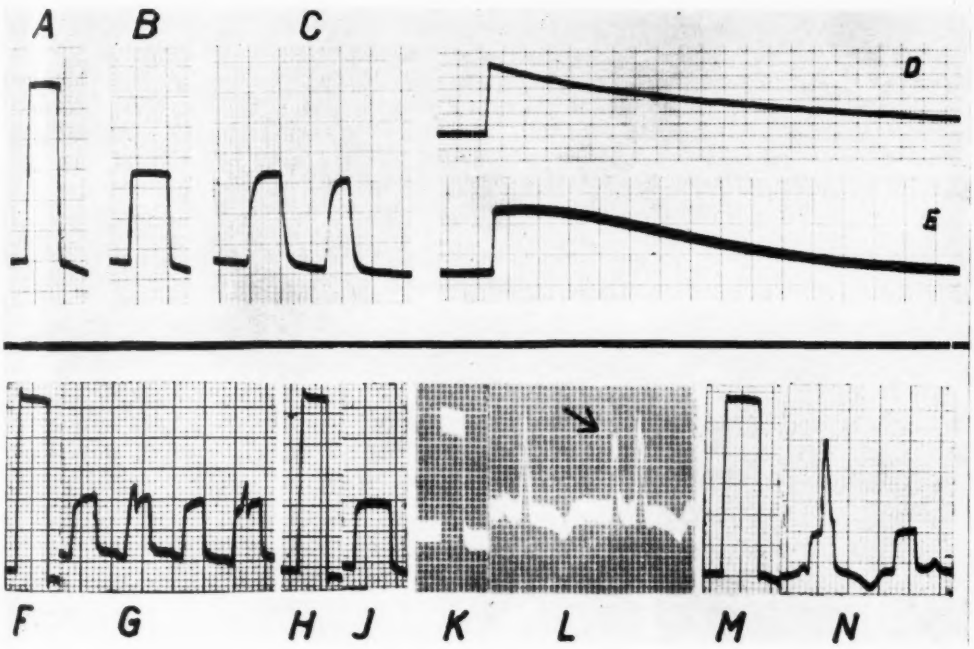

FIG. 2.—Records obtained with the circuit of Fig. 1. The skin of the patients was prepared with the electrode jelly of Jenks and Graybiel (1935).

A, B, C. Experiment on a model circuit: (*A*) record of " e ". (*B*) Connection across a resistance " s "$=5\times10^4\Omega$: record of " v ". (*C*) Same as *B*, but the resistor is paralleled by a condenser of 1μF. *A, B, C* at the same sensitivity setting of the instrument. Resistor " r "$=5\times10^4\Omega$.

D, E. Decay curves: (*D*) short time-constant amplifier. (*E*) Sanborn amplifier.

F, G. Subject P. F.: (*F*) record of " e ". (*G*) Record of " v ". Resistor " r "$=5000\Omega$. " Y "=66·1 per cent. Subject's body resistance, " s "$=2600\Omega$.

H, J. Same subject: the ECG is eliminated as explained in the text. (*H*) Record of " e ". (*J*) Record of " v ". "Y "=64·2 per cent; " s "$=2800\Omega$, coinciding fairly with the previous measurement.

K, L and M, N. Subject M. D.

K, L. Measurement by means of a cambridge string galvanometer. String resistance: 4500Ω. Calculated body resistance: 3100Ω. Further details in the text.

M, N. Measurement with the circuit of Fig. 1: " Y "=77·2 per cent; " s "$=3000\Omega$. Fair agreement between the two methods, as the low skin resistance (electrode jelly) avoids a capacitive overshooting.

The accuracy of the method is not better than 10 per cent for measuring resistance up to $10^4\Omega$ and 15 per cent between $10^4\Omega$ and $2\times10^4\Omega$, corresponding to the unavoidable error of 5 per cent at least when measuring " Y " with a clinical cardiograph (Council on Phys. Med., 1947; Elmqvist, 1939).

EFFECT OF THE ELECTRICAL CAPACITY OF THE SKIN

A discussion of the conducting properties of the skin or an analysis of the skin impedance is beyond the scope of this paper (Einthoven *et al.*, 1922; Schaefer, 1942; Liechti and Stephan, 1944; Lepeschkin, 1947). Yet to show the part played by the skin capacity, a condenser in parallel with a resistor may be put as a load on the source of current, in place of the ohmic resistance only. When rectangular potentials are applied to this capacity-resistance system, it is obvious (Fig. 2 C) that the time of rise of the voltage pulse to the maximum value tends to be prolonged by a time interval

corresponding to the loading of the condenser; the top-level of the wave is, however, the same as the level reached when the connection is made across a resistance only (Fig. 2 B). The method here described can accordingly be used to measure a patient's resistance without errors arising from the skin capacity. This is valid provided that the time constant of the resistance-capacity coupled amplifier used is long enough for the top of the voltage waves, delayed by the capacitive shunt, to be reached before the decay of the tracing. The Sanborn instrument used meets this requirement because of the slow initial rate of decay of its standardization curve (Fig. 2 E) which shows no drop before 0·3 sec., owing to its special compensation circuit (Miller, 1938). An amplifier with too short a time constant (Fig. 2 D), would not be convenient for this purpose (the maximum delay due to skin capacity was found to be 0·12 sec.).

Elimination of the Superimposed Electrocardiogram

When the voltage of the potential divider is applied to the human body, the electrocardiogram is superimposed upon the small rectangular potential waves and the measurement of their magnitude may become difficult (Fig. 2 N). This trouble can be avoided by using a higher voltage and reducing the sensitivity of the amplifier. Unfortunately the commercial cardiographs lose their accuracy at low sensitivity, when too large a voltage overloads their input stage. This condition is easily overcome with a voltage divider, properly shielded, made up of high value resistors (Sanborn, 1949), in order not to modify the input characteristics of the instrument. (With a potential divider of 1 megohm and $5 \times 10^4 \Omega$ in series, 60 mV are reduced to 2·8 mV; 60 mV are supplied by 1000Ω in series with 40Ω instead of 2Ω, in the circuit as shown in Fig. 1.) Fig. 2 G shows the shape of the voltage waves connected across the body, distorted by the electrocardiogram superimposed on the tracing. Fig. 2 H and J, show the tracings produced by the procedure modified as mentioned above, and it may be seen that the electrocardiogram does not appear on the records of the voltage connected across the body (Fig. 2 J).

Summary

A simple circuit was devised for measuring clinically, with an amplifier type of electrocardiograph, the electrical d.c. resistance of a patient. This procedure is based on the shunt of a known voltage through the body and no error arises from the skin capacity. Calculations are quick and the method is easily practised with few accessories to the cardiograph. Brief preliminary mention is made of the part played by the patient's resistance in special electrocardiographic procedures, even in conjunction with an electronic amplifier.

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This investigation was under the direction of Dr. A. Delachaux.

GENERAL ANÆSTHESIA AND CARDIAC INHIBITION

BY

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The occurrence of cardiac inhibition during general anæsthesia is cited as one of the possible causes of sudden death. The facts concerning the subject are few and it is generally accepted that atropine gives adequate protection. The introduction of the intravenous use of prostigmine as an antidote to curare brings into prominence the question of vagal inhibition during anæsthesia, particularly in view of the recent reports of deaths following the simultaneous intravenous administration of atropine and prostigmine (Macintosh, 1949; Clutton-Brock, 1949).

Reid and Brace (1940) reviewed previous reports about the vagal innervation of the heart and lungs and reported the occurrence of cardiac arrhythmias of ventricular and supraventricular forms following mechanical irritation of the trachea of an anæsthetized patient: they suggested that the irritation caused stimulation of the vagal pulmo-cardiac reflexes with resulting changes in the cardiac rhythm, and advised the use of atropine to prevent the disturbances. Adrian (1933) observed that the stretch receptors in the lungs were unaffected by surgical anæsthesia. Brow, Beattie, and Long (1930) reported that stimulation of the peripheral end of the cut vagus abolished ventricular arrhythmias in anæsthetized animals. In a recent investigation, the author (Johnstone, 1950) observed that the ventricular arrhythmias associated with cyclopropane anæsthesia were the result of sympathetic stimulation due to carbon dioxide accumulation in the body during anæsthesia. The arrhythmias could be abolished either by eliminating the carbon dioxide by assisting the respirations or by increasing the irritancy of the inhaled vapours by adding ether. These observations suggest that the ventricular arrhythmias are of sympathetic origin and can be abolished by vagal stimulation.

The object of the present investigation is to determine to what extent the anæsthetic agent stimulates the pulmo-cardiac reflexes by irritating vagal nerve endings in the air passages. Sixty healthy adults with normal cardiovascular and respiratory systems have been selected, their ages ranging between twenty and fifty years. The operations consisted of herniorrhaphies, colporrhaphies, appendicectomies, hæmorrhoidectomies, and hysterectomies. Anæsthesia was induced in each case with half a gramme of thiopentone and maintained on cyclopropane and ether in a Coxeter-Mushin closed circuit machine. A proportion of them received atropine, as described below. No pre-operative sedatives of any kind were given. A simple oro-pharyngeal airway was used in each case and all patients were in either the supine or lithotomy positions. Only those patients in whom the air passages remained perfectly patent throughout anæsthesia have been included, as obstruction of the passages by spasm or mucus causes increase in the pulse rate. Care was taken to prevent pressure by the face mask on the orbits as this may cause reflex inhibition of the heart.

The galvanometer string of a portable electrocardiograph was under constant observation from before induction till five minutes after the removal of the mask. Tracings were taken at intervals throughout each operation, as described below, and a total of approximately three hundred were developed. All the changes noted below have been confirmed by electrocardiograms. I was personally responsible for the administration of the anæsthetics and the observation of the galvano-

meter string in order to establish the closest possible relation between the clinical details of anæsthesia and the changes in cardiac rhythm. All patients recovered uneventfully.

The investigation has been divided into four sections as follows:

(1) The effects of cyclopropane-ether anæsthesia on non-atropinized subjects.

(2) The effects of intravenous atropine during cyclopropane-ether anæsthesia.

(3) The effects of intravenous atropine during cyclopropane-ether anæsthesia with CO_2 accumulation.

(4) The effects of atropine pre-medication on cyclopropane-ether anæsthesia.

Cyclopropane-ether without atropine. Fifteen patients have been investigated, none of whom received any pre-operative drugs. Anæsthesia was induced with half a gramme of thiopentone and maintained on cyclopropane and oxygen in a closed circuit with CO_2 absorption. Any tendencies towards respiratory depression were overcome by gently assisting the respirations. After twenty minutes of cyclopropane anæsthesia the ether was turned on full for three minutes. The mask was then removed and the lungs ventilated with air. Tracings were taken before induction, immediately after the administration of thiopentone, after twenty minutes of cyclopropane anæsthesia, after three minutes of cyclopropane-ether anæsthesia, and one minute after the removal of the mask.

Sinus rhythm was present in each case prior to induction. The administration of thiopentone caused an increase in the rate in ten patients, a decrease in three, and two were unchanged. Marked slowing of the pulse rate occurred in each case during cyclopropane anæsthesia. The lowest rate was 45 a minute, and A-V nodal rhythm was present in three of them. The addition of ether caused further slowing in eleven, four were unchanged in rate, and A-V nodal rhythm appeared in seven more patients. Sinus rhythm was present and there was a marked increase in the rates within one minute after the removal of the mask in every case (Fig. 1). The greatest increase was from 55 (A-V nodal) to 105 (S-A nodal). There was no evidence of ventricular arrhythmias in any of the patients during anæsthesia.

Cyclopropane-ether with intravenous atropine. Bradycardia was induced in fifteen patients by the administration of a mixture of cyclopropane, ether, and oxygen in a closed circuit with CO_2 absorption. No pre-operative drugs were given and sinus rhythm was present in all patients before induction. When bradycardia was established, usually after fifteen minutes of cyclopropane-ether anæsthesia, 1/100th of a grain of atropine, was given intravenously and the anæsthetic continued. Tracings were taken before induction, after fifteen minutes anæsthesia, and half a minute after the injection of atropine.

Complete cardiac arrest occurred in one patient. Sinus bradycardia was present in seven patients and A-V nodal bradycardia in seven during cyclopropane-ether anæsthesia. The administration of atropine was followed, within thirty seconds, by the appearance of sinus tachycardia in each case (Fig. 2). No ventricular arrhythmias were seen in any of the patients with the exception of the case of cardiac arrest that is described below.

Cyclopropane-ether, CO_2 accumulation, with intravenous atropine. Cyclopropane, ether and oxygen were administered to fifteen patients, using a closed circuit, without carbon dioxide absorption. None of them received any pre-operative drugs and sinus rhythm was present in all before induction. The occurrence of ventricular arrhythmias during anæsthesia was prevented by increasing the amount of ether in the inspired mixture. After fifteen minutes atropine, 1/100 gr., was injected intravenously and the anæsthetic continued with the absorber turned on. Tracings were taken before induction, after fifteen minutes of cyclopropane-ether anæsthesia, and thirty seconds after the administration of atropine.

The degree of slowing of the pulse during anæsthesia in this series was considerably less than in the previous series in which CO_2 absorption took place. A-V nodal bradycardia occurred in two, increase in the sinus rate in one, and decrease in the sinus rates in the remainder, the lowest rate being sixty beats a minute. Ventricular arrhythmias appeared in each case within thirty seconds after the injection of atropine, multifocal ventricular tachycardia being present in ten and

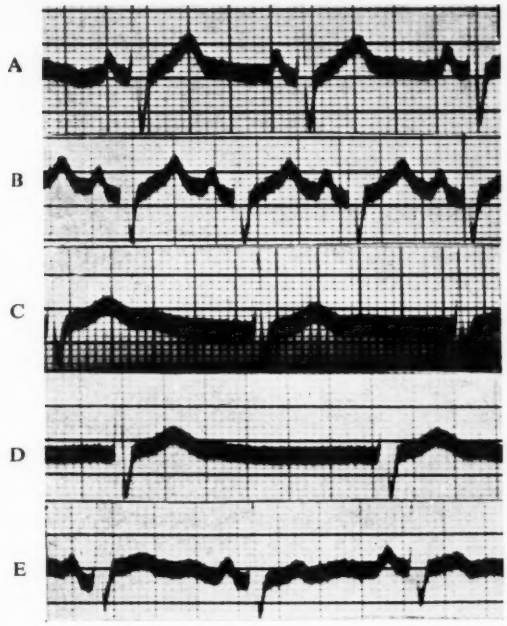

FIG. 1.—Man, 45 years. (A) Before induction. No pre-operative drugs given. (B) Immediately after induction with thiopentone. (C) After twenty-four minutes of cyclopropane anæsthesia with carbon dioxide absorption (D) Ether added to the circuit three minutes previously. (E) Mask removed one minute previously.

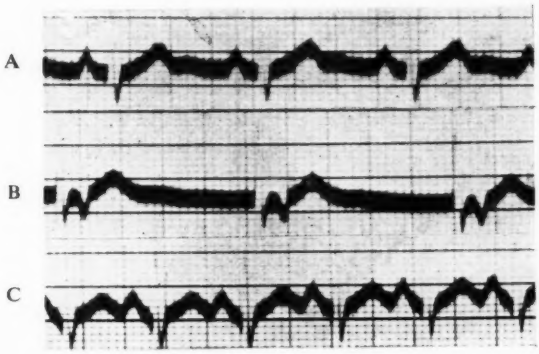

FIG. 2.—Man, 23 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anæsthesia with carbon dioxide absorption. (C) Atropine, gr. 1/100, administered intravenously thirty seconds previously.

bigeminal rhythms in five. The bigeminal rhythms consisted of alternating sinus beats and ventricular extrasystoles, the pulse rate being rapid. The insertion of the CO_2 absorber caused the disappearance of the ventricular arrhythmias within four or five minutes in each case, with the appearance of sinus tachycardias of between one hundred and thirty and one hundred and fifty beats a minute (Fig. 3 and 4).

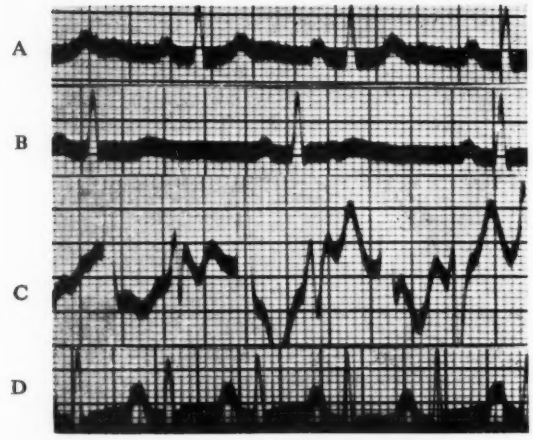

FIG. 3.—Man, 34 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anæsthesia with carbon dioxide accumulation. (C) Atropine, gr. 1/100, administered intravenously thirty seconds previously. (D) Carbon dioxide absorber inserted into circuit three minutes previously.

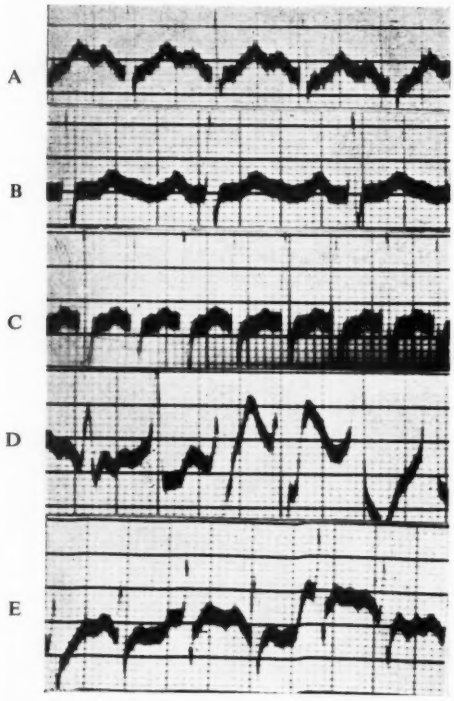

FIG. 4.—Man, 28 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anæsthesia with carbon dioxide accumulation. (C) Atropine, gr. 1/100, administered intravenously fifteen seconds previously. (D) Atropine thirty seconds previously. (E) Carbon dioxide absorber inserted three minutes previously.

Atropine pre-medication with cyclopropane-ether. Fifteen patients undergoing operations for appendicitis, hernia, or hysterectomy received atropine, gr. 1/50, by intramuscular injection twenty minutes before the induction of anæsthesia; sinus rhythm was present in all of them. Anæsthesia was induced with half a gramme of thiopentone in each case and maintained on cyclopropane and oxygen in a closed circuit with CO_2 absorption. Any tendencies towards respiratory depression were overcome by gently assisting the respiration. After twenty minutes of cyclopropane anæsthesia ether was added for a period of three minutes. The mask was then removed and the lungs ventilated with air. Tracings were taken before induction, after induction with thiopentone, after twenty minutes of cyclopropane anæsthesia, after three minutes of cyclopropane-ether anæsthesia and one minute after the removal of the mask.

The administration of thiopentone was followed by an increase in the sinus rate in four patients, a decrease in two, and nine were unchanged. During cyclopropane anæsthesia tachycardia was present in every case, being of sinus origin in thirteen and of A-V nodal origin in two. The addition of ether caused no marked change in the pulse rates but caused pacemaker shift to the A-V node in five more patients. One minute after the removal of the mask sinus tachycardia was present in every case (Fig. 5). No ventricular arrhythmias were observed.

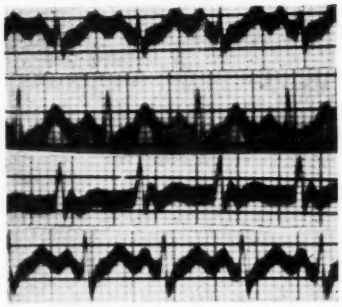

FIG. 5.—Woman, 45 years. (A) Before induction. Atropine, gr. 1/50, given intramuscularly twenty minutes previously. (B) After twenty minutes of cyclopropane anæsthesia with carbon dioxide absorption. (C) Ether added three minutes previously. (D) Mask removed one minute previously.

CARDIAC ARREST DURING ANÆSTHESIA

Cardiac arrest has been encountered in two patients. One occurred in the present investigation and one in a previous work (Johnstone, 1948). Details of these cases are as follows.

Case 1. M.R., 36 years. A healthy, well-nourished woman undergoing dilatation of the cervix and curettage of the uterus for an incomplete abortion. No anæmia. No pre-operative drugs given. Anæsthesia was induced with half a gramme of thiopentone and maintained on cyclopropane and oxygen in a closed circuit with carbon dioxide absorption. After fifteen minutes of cyclopropane anæsthesia the ether was turned on for one minute and the mask was then removed. The pulse became progressively slower from the start of the inhalation anæsthetic and, after sixteen minutes of cyclopropane-ether anæsthesia, complete cardiac arrest occurred and lasted for approximately forty-five seconds. Atropine, gr. 1/100 was injected intravenously a few seconds before the onset of complete arrest. The anæsthetic was then removed and the lungs were flushed out with air by manual pressure on the re-breathing bag. The pulse returned in about thirty seconds and the patient recovered uneventfully. Details of the electrocardiography are shown in Fig. 6. It will be seen that the period of cardiac arrest was followed by a period of ventricular tachycardia. Unfortunately the patient was returned to the ward before this arrhythmia had subsided as her general condition was satisfactory. A tracing taken one hour after the operation showed a normal sinus rhythm at ninety-five beats a minute. At this time the patient was fully recovered.

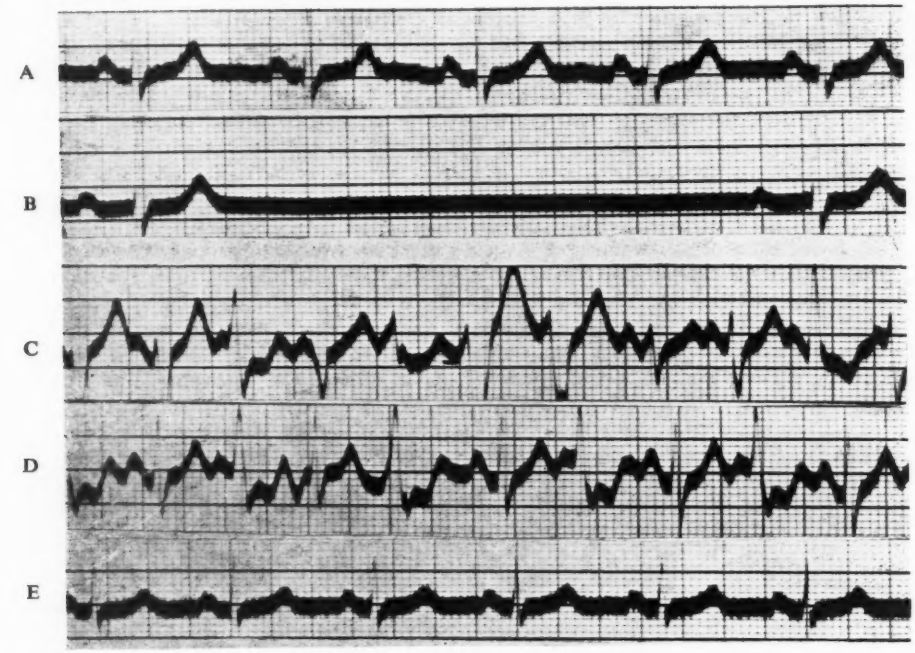

FIG. 6.—Woman, 36 years. (A) Before induction. No pre-operative drugs given. (B) After fifteen minutes of cyclopropane-ether anæsthesia with carbon dioxide absorption. Approximately forty-five seconds of complete cardiac arrest followed the taking of this tracing. (C) One minute after the removal of the mask and the intravenous administration of atropine gr. 1/100. (D) Two minutes after the removal of the mask. (E) One hour after the operation.

Case 2. J.G., 41 years. A healthy, muscular man undergoing herniorrhaphy. No pre-operative drugs given. Anæsthesia was induced with half a gramme of thiopentone and maintained on trichlorethylene, nitrous oxide and oxygen with a Boyle's apparatus. After sixteen minutes of trichlorethylene anæsthesia, the ether was turned on and continued for six minutes. The mask was then removed and anæsthesia discontinued. Details of the electrocardiography are shown in Fig. 7.

During the period of trichlorethylene anæsthesia the sinus rate gradually dropped from one hundred and thirty beats a minute to fifty beats a minute. After the addition of ether for five minutes, complete A-V block occurred with ventricular standstill which lasted for approximately forty-five seconds. The mask was then removed and ventricular contractions re-commenced in thirty seconds. A sinus rate of sixty beats a minute was present three minutes after the removal of the mask. During the period of ventricular standstill the auricles were contracting at forty-five beats a minute and spontaneous respiration was present. The patient made an uneventful recovery.

DISCUSSION

These observations indicate that vagal inhibition of the heart occurs during the inhalation of an anæsthetic, the degree of inhibition varying directly with the irritancy of the inhaled vapour. It is probable that the anæsthetic stimulates sensory nerve endings in the lungs with resulting cardiac inhibition through the pulmo-cardiac reflexes. If the inhibition were due to a more central effect of the anæsthetic there would not be such a prompt reversal of the changes after the removal of the

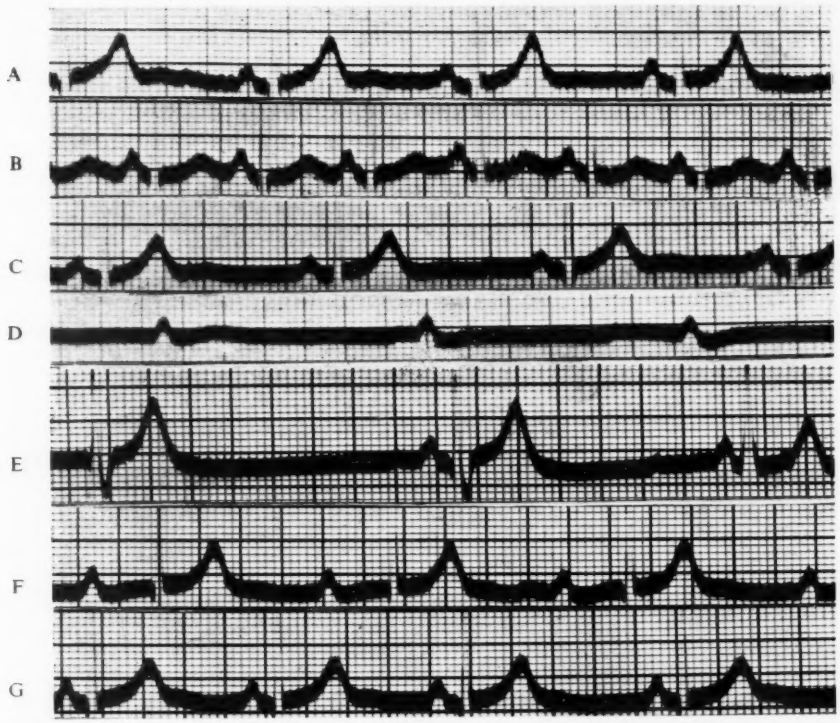

FIG. 7.—Man, 41 years. (A) Before induction. No pre-operative drugs given. (B) Immediately after induction with thiopentone. (C) After ten minutes of trichlorethylene anæsthesia. (D) Ether added six minutes previously. (E) Mask removed half a minute previously. (F) Mask removed one minute previously. (G) Mask removed three minutes previously.

face mask. The arrhythmias to which the inhibition gives rise include sinus bradycardia, A-V nodal rhythm, partial and complete A-V block, ventricular standstill, and complete cardiac arrest.

The pre-operative administration of atropine prevents the more dangerous degrees of inhibition, such as S-A nodal or A-V nodal bradycardia, A-V block, and cardiac arrest. Wilson (1915) pointed out that atropine had a more selective action on the A-V node in protecting it from the effects of vagal stimulation. He demonstrated the occurrence of A-V nodal escape during orbital pressure in atropinized subjects and suggested that the escape occurred because the " period " of the S-A node was depressed below the " period " of the A-V node with the result that the latter node became the pacemaker. My observations indicate that a similar reaction occurs during anæsthesia. Best and Taylor (1927) have stated that $\frac{1}{20}$—$\frac{1}{15}$ of a grain of atropine, is required to annul completely the effects of vagal stimulation in man. This probably accounts for the high incidence of A-V nodal rhythm during anæsthesia when smaller doses of atropine are given pre-operatively.

The pre-operative administration of atropine in doses up to, gr. 1/50, protects most patients from serious cardiac inhibition during anæsthesia. I have, however, observed bradycardia and partial A-V block during the induction of anæsthesia with ether in a jaundiced patient who had received atropine, gr. 1/50, pre-operatively. Sprague (1929) has reported the progressive slowing of the pulse to complete cessation and death of a jaundiced patient induced with ether. It is important, therefore, to watch carefully for the patient with increased vagal tone, e.g. patients with jaundice, simple sinus bradycardia or peptic ulceration. High concentrations of anæsthetic vapours should

be avoided in such patients. Judging from preliminary observations, it is probable that atropine, gr. 1/100 intravenously gives protection for approximately thirty minutes and atropine, gr. 1 50 intramuscularly for ninety minutes after administration.

In addition to releasing the S-A and A-V nodes from the effects of vagal inhibition during anæsthesia, the intravenous administration of atropine to anæsthetized subjects may release the ventricular centres and give rise to the serious complication of ventricular tachycardia. This complication is particularly liable to occur in patients in whom carbon dioxide has been allowed to accumulate during anæsthesia. Auricular tachycardia sometimes precedes the onset of ventricular tachycardia by a few seconds but I was unable to verify this point fully as the facilities for continuous photography were not available. I obtained a tracing in one patient (Fig. 4C). In this investigation the rise in carbon dioxide tension was deliberately induced by excluding the absorber from the circuit. A similar rise may occur after prolonged deep anæsthesia, particularly in curarized patients, when respiration has been depressed and no effort made to assist the respiratory exchange by rhythmic manual compression of the re-breathing bag.

Dameshek *et al.* (1938) have observed the occurrence of sinus and ventricular tachycardias in some patients after subcutaneous administration of acetyl-B-methylcholin chloride. They suggested that this action was probably due to stimulation of the cholinergic sympathetic ganglia. It may be assumed that the intravenous use of prostigmine may sometimes have a similar action. Thus, the simultaneous intravenous administration of atropine and prostigmine to anæsthetized subjects may release a sympathetic stimulation of sufficient intensity as to precipitate a fatal ventricular fibrillation. This may have been the mechanism of the sudden deaths to which I referred at the beginning of this paper. On the other hand, the cardiac failure may have been caused by vagal inhibition due to the action of prostigmine, as atropine, gr. 1/100, would not give complete protection from a sudden para-sympathetic stimulation.

The important point established by this work is that the simultaneous intravenous administration of atropine and prostigmine to anæsthetized patients is a dangerous procedure. The only way in which this danger can be overcome is to give minimal doses of curare and thereby eliminate the need for prostigmine. There is no doubt that the judicious use of curare is of considerable benefit to anæsthesia as it reduces the amount of anæsthetic required, particularly in abdominal surgery. The use of this drug does not eliminate the necessity for moderately deep anæsthesia in order to inactivate the laryngeal reflexes. Wright (1940) stated that the drug has no effect on the vagus. Laryngeal or bronchial spasm may therefore occur in lightly anæsthetized patients. The effect of curare on these spasms is merely to mask the straining which ordinarily occurs in the respiratory musculature.

I have used curare extensively for abdominal surgery and in no case has it been found necessary to administer a second dose after the initial 15 mg. The curare is given intravenously as soon as the patient is in the first plane of surgical anæsthesia and the laryngeal reflexes have been abolished. The relaxation which this amount of curare produces can be maintained indefinitely with cyclopropane and a trace of ether. It is perfectly safe and easily reversible. This procedure eliminates the need for prostigmine in so far as abdominal surgery is concerned. Adequate oxygenation must be maintained by manually assisting the respiration. Mautner and Luisada (1941) have observed that oxygen lack tends to neutralize the effect of curare on voluntary muscle in animals.

It will be noted that A-V nodal rhythm occurs frequently during anæsthesia in patients to whom the usual dose of atropine has been given pre-operatively. The influence of this arrhythmia on the cardiac output is unknown. Its presence can only be recognized with accuracy by the direct observation of the galvanometer string of an electrocardiograph. It can be recognized sometimes by observing the synchronous pulsations of the carotids and jugulars. I have auscultated a few cases and there was a marked decrease in the intensity of the heart sounds during the periods of A-V nodal rhythm. During anæsthesia, A-V nodal rhythm can be abolished, with the return of sinus rhythm, either by decreasing the concentration of the inhaled vapours or by using a less irritant agent.

True bradycardia during anæsthesia must be carefully distinguished from an apparent bradycardia due to alternating interpolated ventricular extrasystoles which are not conducted to the peripheral arteries. This differentiation is important as the latter arrhythmia can be abolished by assisting the respiration or by adding ether whereas this procedure will aggravate a true bradycardia and may precipitate a cardiac arrest.

It is concluded that it is essential to use an electrocardiograph during anæsthesia in patients with myocardial disease or during prolonged operative procedures. It is well worth the extra trouble as, if a regular sinus rhythm is maintained throughout at between one hundred and one hundred and thirty beats a minute, the recovery of the patients from anæsthesia will be rapid and uneventful. Auricular fibrillation appears to be uninfluenced by general anæsthesia, but the tendency towards the occurrence of ventricular arrhythmias remains unaltered and these arrhythmias can be controlled in the manner already described. The dangers associated with the administration of an inhalation anæsthetic to an inadequately atropinized patient have been illustrated. This may explain the sudden deaths that have been attributed to status lymphaticus.

The influence of thiopentone on cardiac rhythm and on the cardiac arrhythmias will be discussed in a future paper.

Summary

An electrocardiographic study has been carried out on sixty healthy subjects. It has been demonstrated that cardiac inhibition, to the point of complete cardiac arrest, may occur as the result of inhaling cyclopropane or ether. The degree of inhibition varies directly with the irritancy of the inhaled vapour.

The inhibition of the heart appears to be due to stimulation of vagal nerve endings in the air passages by the anæsthetic agent. The stimulation causes reflex inhibition of the heart through the pulmo-cardiac reflexes.

Atropine will prevent the more serious degrees of inhibition in all except the most vagotonic subjects. Doses of 1/50 of a grain or less do not prevent the occurrence of A-V nodal rhythm during anæsthesia.

The intravenous administration of atropine to anæsthetized subjects in a state of increased CO_2 tension may cause ventricular tachycardia. It has been suggested that the simultaneous administration of atropine and prostigmine may potentiate the sympathomimetic effect of atropine, with fatal results.

It has been advised that the muscular relaxation obtained with the initial dose of curare should be maintained by anæsthetic agents and not by the administration of more curare, in so far as abdominal surgery is concerned. This procedure eliminates the need for prostigmine.

The more frequent use of the electrocardiograph during anæsthesia has been advocated.

I wish to express my gratitude to Mr. E. S. Gawne, F.R.C.S., for granting me permission to carry out this investigation and for his co-operation during the experiments.

I should also like to thank Messrs. Tytherington Products Ltd., of Cheadle Cheshire, who are producing a combined anæsthestic apparatus and electrocardiograph in conjunction with Messrs. A. C. Cossor of London.

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THEOPHYLLINE-ETHYLENEDIAMINE IN THE MEASUREMENT OF BLOOD CIRCULATION-TIME

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In the past few years, the surgical treatment of congenital cardiac abnormalities has led to a fresh interest in the measurement of blood circulation-time as a diagnostic aid (Allanby, 1949). Old controversies on the relative value of different methods have also been revived, so the time may be opportune for the description of an accurate method suitable for routine use in a busy out-patient department. The many methods that have been devised are based on the introduction into the blood stream at one point, of a substance that is detectable at another point by one or more of its physical or pharmacological properties.

The property of producing an intense taste in the mouth is the feature of the popular arm-tongue tests of Winternitz and his colleagues (1931) using the bitter decholin, and of Fishberg and his colleagues (1933) using saccharin: these tests have an entirely subjective end-point, and were therefore excluded in favour of others having an objective termination. The most accurate of the objective methods is that of Blumgart and Yens (1927) who used a radioactive salt which could be detected at various points by a special instrument; a simple method was devised by Fishback (1941) who injected a solution of fluorescein and observed the palpebral conjunctiva, under ultra-violet light in a dark room, for the first appearance of a brilliant yellow colour. Such methods require too much apparatus for our purposes, so our attention was directed upon the " histamine flush test " introduced by Weiss *et al.* (1929) in which an injected histamine solution produces a dilatation of the minute vessels of the face, noticeable to the observer as a flush: in an English trial of this method, Bain (1934) found that the injection of histamine could produce serious and perhaps fatal reactions.

In an interesting group of tests with an objective end-point the injected substance is a respiratory stimulant and produces a sharp increase in the depth of breathing, readily noticeable by the observer. The first substance to be used in this way was sodium cyanide, which was introduced by Loevenhart and his colleagues (1922) in the course of animal experiments, and was tried in man by Robb and Weiss (1933). Similar methods were devised by Berliner (1940), using alpha-lobeline, and by Elek and Solarz (1942), using papaverine, but were found to be unreliable.

In an effort to prevent atalectasis occurring in surgical cases as an early post-operative complication, Sperling, Weisman and Papermaster (1942) gave intravenous injections of theophylline-ethylenediamine, and found that these produced a sudden increase in the rate and depth of respiration. Koster and Sarnoff (1943) observed so marked an increase in respiration, in many cases amounting to a gasp, that they decided to use it to measure the circulation time from the arm to the respiratory centre. Their series of 72 cases consisted of patients of both sexes and of all ages from 12 to 82 years, after operations, and in only one instance was there difficulty in recognizing the end-point: they did not take duplicate readings and the test was not performed on patients with cardiovascular, metabolic, or blood diseases.

For our purposes, a method of circulation-time measurement was required that would be

safe and efficient, simple, and speedy to perform, and would not demand expensive or elaborate equipment: our attention, therefore, was concentrated on those methods based on respiratory stimulation. Previous work on the alpha-lobeline and papaverine tests did not suggest that they were likely to be satisfactory, so we were left with a choice between the cyanide and theophylline-ethylenediamine methods—neither of which had been given an extensive trial in this country. Since the cyanides are such notorious poisons, it seemed unwise to use one of them for intravenous injection in a routine test while there was a reasonable alternative. It was decided then, to select theophylline-ethylenediamine, which had the additional advantage of being available commercially in sterile solution in convenient ampoules.

As has been stated, Koster and Sarnoff tried their new method in a relatively small number of normal cases only; it was necessary, therefore, before adopting the test for routine use, to give it a thorough trial in a larger number of normal subjects and in others suffering from those disorders that are known to affect the blood circulation time.

Clinical Trials of the Theophylline-Ethylenediamine Test

In this investigation, theophylline-ethylenediamine solution was used in the form of the proprietary cardophylin, which is available in ampoules of 2·0 ml., containing 0·48 g. of the drug: since the dose is 1·0 ml., an ampoule is often sufficient for two tests.

The syringe is charged, a tourniquet is applied to the right upper arm of the recumbent patient and an antecubital vein is entered; the tourniquet is released and, after a delay of a few seconds for the readjustment of the venous blood-flow, the syringe plunger and stopwatch cap are pressed simultaneously. The watch is stopped whenever the end-point occurs.

In order to avoid discrepancies, a 10 ml. syringe was always used, with a gauge 1 needle, for these make it possible for the 1 ml. of solution to be injected very rapidly, and since the piston stroke is only about 0·5 cm. the syringe is easy to control. After some practice, the investigator finds no difficulty in manipulating the syringe with his right hand and the stop-watch with his left, but an assistant may take the watch.

The Circulation-Time in Normal Subjects

In this part of the trial, the routine test was performed on 150 subjects who were normal in that they did not suffer from diseases of the heart, of the blood, or of metabolism: they were typical adult hospital patients, of all ages, from the wards and out-patient clinics. The results (summarized in Table I) ranged from 6·8 to 22·0 seconds, with a mean of 12·1 and a standard deviation of 2·3 seconds.

TABLE I

Results in Control Subjects

No. of Cases	Test	Circulation-time (seconds) Range of Readings	Remarks
150	single	6·8–22·0	Mean value 12·1 seconds. Standard deviation 2·3.
50	(*a*) first (*b*) second (*c*) difference	7·8–19·6 6·8–20·8 0– 2·6	Mean difference between first and second readings 1·1 seconds.

In order to find if the circulation-time is reasonably constant in the same subject, duplicate measurements were made in a further group of 50 normal subjects. Although maximum accuracy could be obtained only by performing each test under strictly basal conditions, these are unobtainable in general practice, hence the tests were made under normal ward conditions, with an interval of several days between the two. The results, which appear in Table I, show that the differences

between first and second measurements range from 0 to 2·6 seconds, with a mean difference of 1·1 seconds.

In the 250 tests on 200 normal subjects there was no evidence of any constant relation between blood circulation-time and the subject's age, weight, pulse rate, or blood pressure: these details are omitted from the tables for the sake of simplicity.

Although the end-point is usually a sharp, deep inspiration amounting to a gasp, this may be preceded by a swallowing movement, a sudden change in facial expression denoting anxiety, or a catch in the breath during expiration. There is a temptation to wait for the dramatic gasp, but since it does not occur in a small percentage of tests, the first observable change should be regarded as the definite end-point (see Table II). In no case was there any dangerous reaction, but most

TABLE II

END-POINTS OBSERVED IN NORMAL SUBJECTS

Type	Description	No. of Cases	Percentage
1	Inspiratory gasp	224	89·6
2	Swallowing movement	15	6
3	Change in expression	9	3·6
4	Catch in the breath during expiration	2	0·8
		250	100

subjects spoke of a feeling of warmth over the face and of a light-headedness lasting for about half a minute: these side-effects were more prominent in excitable subjects, usually women, and in 8 cases—all confirmed psychoneurotics—they produced a violent emotional upset, with weeping, trembling, and tachycardia. Local reactions occurred only in the very few cases in which there was some leakage of the solution round the vein: this caused severe pain at the site of the leakage but was not followed by necrosis or thrombosis.

CIRCULATION-TIME IN THYROTOXICOSIS

These measurements were made under normal ward conditions, and the results of 33 tests in 21 cases are shown diagrammatically in Fig. 1 and in Table III.

Of 18 tests in these cases of hyperthyroidism, which had not been treated in any way, the circulation-time measurement ranged from 5·6 to 13·6 seconds, with a mean of 7·1 seconds. In the cases under treatment by thiouracil, or its derivatives, the measurements were appreciably higher, and successive tests showed that clinical improvement was paralleled by a rise in the circulation-time.

CIRCULATION-TIME IN DISORDERS OF THE BLOOD

The results of 41 tests in 29 cases of anæmia and two cases of polycythemia are shown in Fig. 1 and in Table III.

Comparison with blood count figures showed that the circulation-time was roughly parallel to the hæmoglobin level, and successive tests confirmed that an increase in that level was usually accompanied by an increase in the circulation-time.

CIRCULATION-TIME IN CARDIOVASCULAR DISEASE

In this series, 108 tests were performed in 85 cases, which were grouped as follows;

(1) Hypertension uncomplicated by cardiac or renal failure—8 cases.

(2) Rheumatic carditis—7 cases.

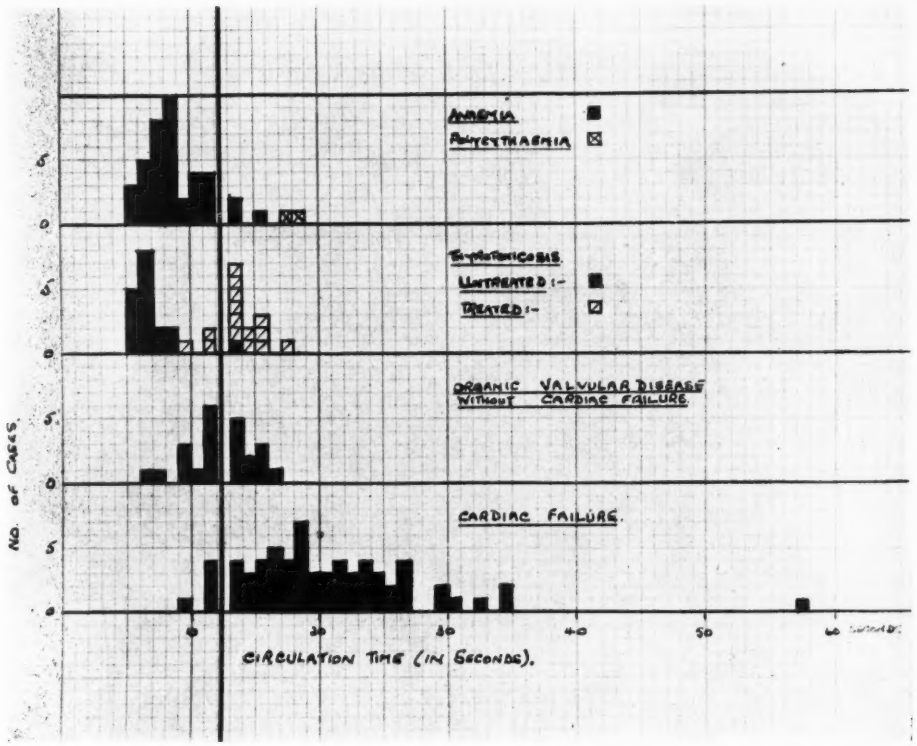

FIG. 1.—Diagram showing distribution of readings in the commoner conditions influencing circulation-time. Heavy vertical line at " normal mean " reading of 12·1 sec.

TABLE III

Condition	No. of Tests	Circulation-time in seconds	
		Range of readings	Mean
Anæmia	39	6·0–15·9	9·2
Polycythæmia	2	17·6–19·0	18·3
Thyrotoxicosis:			
Untreated	18	5·6–13·6	7·1
Treated	15	10·0–17·4	14·0
Hypertension without cardiac failure	9	10·0–17·0	12·8
Valvular disease without cardiac failure	23	6·2–16·4	12·4
Rheumatic carditis	11	7·6–17·0	10·4
Cardiac failure:			
(*a*) Left ventricular	25	15·8–35·0	21·0
(*b*) Right ventricular	40	13·0–58·0	21·0

(3) Organic heart disease without clinical evidence of cardiac failure—22 cases, of which 14 had uncomplicated valvular lesions and 8 had been apparently cured of subacute bacterial endocarditis.

(4) Clinical cardiac failure—48 cases, failure predominantly left ventricular in 19, and right ventricular in 29.

The detailed results appear in Table III, and groups (3) and (4) are represented in Fig. 1. Successive tests in individual cases showed that deterioration or improvement in the clinical condition was accompanied by a corresponding rise or fall.

Summary and Conclusions

The commoner methods of blood circulation-time measurement have been reviewed, and the theophylline-ethylenediamine test was selected for clinical trial.

Extensive trials—involving 432 tests on 337 cases—are described and the results indicate that this method, which has the advantage of having an objective end-point, is safe, simple, and reliable, and eminently suitable for routine use.

In assessing the reliability of the test, the normal mean reading is almost identical with that of Fishberg's saccharin method—probably the most widely used of all—and duplicate readings correspond more closely than in the latter's series (Fishberg *et al.* 1933), being within physiological limits as shown by Stewart (1921). Satisfactory results were obtained from single and repeated tests in patients with anæmia, thyrotoxicosis, and cardiac failure.

This investigation was conducted during my tenure of a Research Assistantship in the University of Bristol, and I wish to record my thanks to the Physicians of Bristol Royal Infirmary for access to their cases, and to Professor C. Bruce Perry for his interest and encouragement.

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POSTURAL HYPOTENSION: THE LOCALIZATION OF THE LESION

BY

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Since postural hypotension was first described by Bradbury and Eggleston in 1925, many reports have been published of patients in whom a great fall in blood pressure occurred on standing. In such cases the blood pressure is usually normal while the patient is horizontal, but falls progressively as he approaches the standing position, and does not rise again until he once more reclines. The cases fall into two groups. In one the disorder is associated with disease of the nervous or endocrine systems, and may be termed symptomatic postural hypotension. In the other no gross evidence of disease is found : some 36 reported cases are of this type, which, as suggested by Bradbury and Eggleston, appears to be a clinical entity to which the term idiopathic postural hypotension may be applied.

Patients with either type of postural hypotension may show similar features. With the great fall in blood pressure that occurs on standing erect, there is often no change in pulse rate, and syncope may occur but is unassociated with nausea and immediately relieved by lying flat. Anhidrosis, frequently patchy in distribution, and nocturnal polyuria are usual in the idiopathic type, and loss of libido may occur. As these features are sometimes found in cases of the symptomatic type, the diagnosis of idiopathic postural hypotension depends on the exclusion of known causes.

The disorder of function responsible for idiopathic postural hypotension has not yet been established beyond dispute. In 1941 Stead and Ebert, and Jeffers *et al.*, independently attributed the postural hypotension to a failure of reflex vasoconstriction in response to a fall in blood pressure. They measured the blood flow in the finger or hand and found a rate that they thought higher than normal for a comparable fall in blood pressure. They inferred from this that the normal vasoconstriction had not occurred in the limbs of their cases of postural hypotension. Barcroft and Edholm (1945), however, have shown that the hand blood flow during the very low blood pressures of the vasovagal reaction of Lewis may be as high or higher than that reported by Stead and Ebert in postural hypotension, and so no certain conclusion may be drawn from observations of blood flow. Vasomotor reflex activity in response to other stimuli also fails to provide indisputable evidence, for Stead and Ebert found that their case showed normal vasoconstriction in response to pinching, while Jeffers *et al.* could not demonstrate any response to a loud noise.

In this paper observations on three cases of idiopathic postural hypotension are reported, and it is concluded that the fall in blood pressure is due to a central failure of reflex vasoconstriction.

The first case has been observed over four years and her history is given at some length as changes occurred in her condition during this time which have not been previously described in this disease.

Case 1. Mrs. A. M., aged 54, was first seen in February, 1946. Three years previously she began to have attacks of giddiness lasting for a few moments while out walking, and would cling to a tree or lamp post for support. She said she had not sweated since that time, although previously she sweated normally, for example, while she was about her housework. Eighteen months later she fainted without warning in the

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street, and since then had fainted frequently, always while erect and especially if she stood still. The frequency and ease with which she fainted varied considerably from day to day, but she had noticed no relation either to the temperature or time of day. Apart from faint pigmentation of the abdomen resembling vitiligo, which had first been noticed 18 months before, no abnormality was found on routine examination. Her blood pressure supine was 160/90 mm. Hg. When she sat up in bed it fell in three minutes to 100/70.

Addison's disease was thought to be excluded by the normal serum sodium and potassium and by a normal water excretion test. The Wassermann reaction was negative and in the absence of any abnormal signs in the nervous system a diagnosis of idiopathic postural hypotension was made.

The postural hypotension persisted throughout four years' observation, and the variation in the ease with which syncope might come on was constantly present. At times when the patient felt " no good " she walked slowly about dragging her feet along, her manner was languid, and she became dizzy after walking up five or six steps. When she was " all right " her step was firm, her manner brisk, and she walked upstairs confidently. Until August, 1948, these variations occurred without warning or associated phenomena, but after that month the patient found that when she was all right her hands and feet felt hot and she could feel sweat on the palms of the hands, over her nose and most of her forehead. This was confirmed in April, 1949, when she was examined in her well phase. Her face and hands were found to be warm though her face had its customary pallor, her palms were moist, and her face slightly sweaty, particularly over the forehead and nose. The skin had been examined several times previously in hot weather or after syncope for the presence of sweat, and these areas had always been found to be dry. Two sweating tests had been performed, and although profuse sweating had occurred elsewhere, these areas had on both occasions been free from sweat. On standing the usual fall in blood pressure occurred. This appearance of sweat on her hands and face with a feeling of heat was so reliable a sign that she was not likely to faint that she was in the habit of waiting for it before venturing out of doors. These episodes of well being usually lasted for a few hours, sometimes all day, and were quite unpredictable in their appearance. The onset was usually clear-cut, for example, once while sitting by the fire, the feeling of warmth came on, she found her hands and face moist, and she went to the cinema; while there the episode passed and she fainted in the foyer on leaving.

Another change of some interest was found in April, 1949. On all previous occasions a marked fall in blood pressure had been accompanied by an increase of pulse rate from about 70 to about 115 a minute. Now a bradycardia occurred. After two hours horizontal the blood pressure supine was 200/105, the pulse rate 72. On sitting up in bed these figures fell to 140/90 and 68, and on standing, fellfurtherto 95/50 and 60.

Symptomatic relief was obtained by a tight abdominal binder and the " head-up " bed regime (MacLean and Allen, 1940), the patient not lying horizontal at any time by day or night, and sleeping on a bed whose head is blocked up. The effects are easily reversible, and it was frequently found that even a few hours supine caused a return to the previous state (MacLean and Allen, 1940). Even in her phases of feeling "all right " she was liable to faint if she had been sleeping horizontal. The observation that the head-up bed regime greatly slows the fall in blood pressure on standing (MacLean, Allen, and Magath, 1944) was repeatedly confirmed, the pressure taking about ten minutes to fall as far as it would fall in two to three minutes without treatment.

Case 2. Mrs. N. W., aged 67, had been in good health until ten years before when she began to have attacks of giddiness, leading to syncope if she did not sit down. At first they occurred only on odd days with months of freedom between, but for some years she had been having two to three " bad days " when syncopal attacks were very frequent, followed by two to three weeks when she could walk about a little, although she had to sit down often. She could not stand still for more than a few seconds at any time, and did her housework from a chair. Fainting usually occurred on first getting out of bed, and was less frequent later in the day. Attacks were more common in hot weather. She did not remember ever having sweated.

No abnormality was found on physical examination. While supine her blood pressure was 130/80; on sitting up in bed it fell in two minutes to 80/55, and on standing a further fall to 60/45 occurred. The pulse rate increased from 82 to 88 a minute. Her serum sodium and chloride were normal, Hb 80 per cent and blood urea 53 mg. per 100 ml. Some improvement was obtained from elastic stockings and a tight abdominal binder, but the head-up bed position caused no change in her condition.

Case 3. Mr. W. H., aged 57, For 3 years he had had attacks of blurring vision while standing or walking, and for 2 years transient dizziness while erect without loss of consciousness. These occurred once or twice a week, and were more likely to come on when he was standing than walking. For 6 months attacks of loss of consciousness had occurred at infrequent intervals, always coming on when standing still. He frequently felt dizzy, but would avoid fainting by sitting down and putting his head between his knees. Attacks were more frequent early in the day, and he had noticed that on some days he felt very well with little tendency to faint, while on other days he was " no good for anything ." For about one year he had been easily tired. He thought he had been sweating less recently. He had had no sexual intercourse for 4 to 5 years, and his erections and emissions had been feeble for 9 months and absent for 4 or 5 months. His wife was a chronic invalid.

He appeared a healthy, rubicund countryman. Routine physical examination revealed no abnormality except varicose veins in the right leg apart from the effect of change of posture on the blood pressure. While supine the blood pressure was 140/85, pulse rate 64 ; on sitting up 120/75, pulse 84 ; when erect after 3 minutes, 55/?, pulse 112.

His serum potassium, serum sodium, blood cholesterol, and blood urea were normal. The Wassermann reaction and blood count were also normal.

The head-up bed position seemed to be beneficial, but the period of observation was not enough to permit a certain opinion of its value.

Change of posture had a similar effect in all cases. On standing the rate and depth of respiration increased as the blood pressure fell, until, with a systolic pressure of 60 mm. Hg, the respiratory rate was usually between 25 and 30 a minute. Dizziness was complained of, and the first case often noticed that her mouth was dry. If the erect position was maintained a coarse tremor next appeared, affecting the left hand in the first case, and all four limbs in the second. In the third no tremor was noted, but a hoarse cry preceded the onset of syncope. In the first case the respirations became noisy and grunting after some minutes, but in the others this was not so evident. Finally, syncope occurred after a time varying from 2½ to 20 minutes. All cases said that loss of consciousness was preceded by visual upsets: in the first " everything went black," but the second noted first blurring of the vision, then a heliotrope hue, and finally white; the third noted blurring of vision. All three had learned to avert syncope whenever dizziness came on by sitting down quickly, but attacks might occur without warning. None had noticed nausea ; nor did yawning, belching or vomiting occur. In the first case electrocardiography showed that the heart rate was not slowed during syncope. No record of the pulse or heart rate was obtained during syncope in the others, but the heart rate was not slowed immediately before or after syncope. During syncope no pulsation could be felt in the carotid or radial artery of any case, and the heart sounds were inaudible.

OBSERVATIONS

Other procedures besides change in posture caused abnormal changes in blood pressure. The excessive fall in blood pressure caused by glyceryl trinitrate (Jeffers *et al.*, 1941) and by reactive hyperæmia (Stead and Ebert, 1941) was shown to occur in the first case investigated, and in all these the same effect was produced by trapping blood in the lower limbs by inflating cuffs round the thighs to diastolic pressure. The volume of blood trapped in the legs of the first case in this way was estimated to be approximately 1·9 and 1·8 litres on two occasions by the method of Smirk (1933). This was found to be within normal limits, and agrees with the observation of Stead and Ebert that in two of their cases the volume of blood present in the lower limbs when the patients were upright was normal. The results are shown in Table I.

Failure to regulate the blood pressure could be shown in other ways. For example, blowing a mercury column up to 40 mm. with the glottis open (Flack, 1921) caused a fall in blood pressure while the patient was supine as in the case described by East and Brigden (1946) ; and, in the erect position, dizziness after a few seconds, and syncope after about 10 seconds, in all cases (Maclean and Allen, 1940). Even taking a moderately deep breath and holding it without straining caused a fall in blood pressure of 15 to 40 mm. Hg systolic when the subject was supine, and the rapid onset of dizziness if erect.

It is clear from what has been said that the sequence of events differed from that in ordinary fainting attacks. Thus, in postural hypotension the blood pressure fell to low levels within two minutes of standing, and remained low while the subjects stood. The increase in pulse rate in two cases when the blood pressure fell, the absence of slowing of the heart rate in syncope in Case 1 and the absence of arterial pulses in all cases during syncope also differed from the findings in fainting (Lewis, 1932). The sudden fall of blood pressure in fainting has been shown to be due to vasodilatation in muscle (Barcroft and Edholm, 1945). The muscle blood flow in postural hypotension has

TABLE I

EFFECT ON BLOOD PRESSURE OF POOLING BLOOD IN THE LEGS

	Blood Pressure		Pulse Rate		Blood Pooled
	Initial	After Pooling	Initial	After Pooling	(litres)
Case 1	190/105	140/85	76	78	1·9
	140/80	85/50	74	95	
	140/85	95/65	80	90	
	160/90	110/70	74	82	
Case 2	115/80	75/55	76	80	
	130/90	100/?	72	72	
Case 3	115/75	100/70	69	74	
	130/90	105/65	56	56	
Controls 1	105/60	95/70	74	80	
2	105/60	100/60	68	78	
3	130/80	135/80	78	84	1·2
4	100/70	100/70	62	66	0·9
5	145/70	145/70			1·9

not previously been recorded, and it was therefore measured in Cases 2 and 3 to see if a similar vasodilatation in muscle might be the cause of the low blood pressure in postural hypotension. A fall in blood pressure, whether caused by change in posture, trapping blood in the legs, or both, was accompanied by a fall in muscle blood flow on all occasions except one. From these experiments it was only possible to say that the response differed from that in fainting in which the muscle blood flow increases as the blood pressure falls, for the change in blood pressure made it impossible to decide whether the blood vessels had altered their diameter. In one experiment, however, although the systolic pressure was reduced to 45 mm. Hg by sitting the patient up and trapping blood in the lower limbs, the forearm blood flow was unaltered. This experiment showed that some vasodilatation might occur, although not of the same order as that found in ordinary fainting.

An immediate and lasting fall in blood pressure on standing, like that found in cases of postural hypotension, may follow carotid sinus denervation (Capps and de Takats, 1938) or extensive sympathectomy. In both of these the carotid sinus reflex arc is disturbed, in the first case at its origin, in the second by severing the efferent nerves to the blood vessels of the viscera and lower limbs. Further, the effect of pressure on the carotid sinus in seven cases of postural hypotension has been reported (Table II). Only in the case of Agostoni is there a doubtfully significant response. In the three cases reported here direct pressure on either carotid sinus had no effect on pulse rate or blood pressure. Although pressure on the carotid sinus is without effect in 30 per cent of normal subjects (Weiss and Baker, 1933) this uniformity in idiopathic postural hypotension is highly significant, and with the similarity in the change in blood pressure on standing to that found in lesions affecting the carotid sinus reflex arc points directly to some lesion of that arc. Additional evidence was obtained by occluding the carotid arteries on one side or the other in Cases 1 and 2. This also failed to provoke any change in pulse rate or blood pressure. The parts of the carotid sinus reflex arc were therefore tested individually as far as possible.

The integrity of the peripheral sympathetic nerves was shown by a normal goose-skin response to faradism in all three cases, and all showed a normal rise in skin temperature with flushing of the skin on blocking the ulnar nerve with local anæsthetic. The peripheral sympathetic nerves were therefore functioning, and the peripheral vessels subject to vasomotor impulses travelling by the

usual peripheral paths. Further evidence of vasomotor activity was a normal rise of skin temperature on heating the body obtained in all three cases. A similar response to heat has been recorded by Jeffers *et al.* (1941).

TABLE II
CAROTID SINUS PRESSURE

Authors	Effect on : Pulse Rate	Blood Pressure
Cappacio and Donald (1938)	Nil	S. up 10 mm. Hg.
Jeffers *et al.* (1941)	Nil	S. down 10 mm. Hg
Agostoni (1937)	Nil	S. down 20 mm. Hg
East and Brigden (1946)	Slight slowing	Nil
Korns and Randall (1937)	Nil	Nil
Moretti (1934)	Nil	Nil
Davis and Schumway-Davis (1937)	No carotid sensitivity	

In all three cases a normal diminution in finger volume and blood flow followed a deep breath. This is known to be a spinal reflex (Gilliat *et al.*, 1948) with a sympathetic efferent path (Bolton *et al.*, 1936). The sympathetic efferent nerves were therefore intact as far as the spinal reflex level.

The higher reflexes were then investigated. In all three cases, as in those described by Jeffers *et al.*, and by Stead and Ebert, a fall in blood pressure was associated with a reduced blood flow in finger and hand, but these changes were within normal limits, and cannot be accepted as evidence of failure of vasoconstriction. Clear evidence of loss of reflex vasoconstriction was obtained by the response to other stimuli.

The effect of cold and pain and sudden noise was investigated in all the patients. For example, Case 1 lay down clothed, and was covered by blankets. After half an hour a plethysmograph was fitted to the right hand and an electric blanket placed round the right arm and forearm. After a further 30 minutes recording began. Room temperature was 19° C., the plethysmograph temperature 34° C. Immersion of the left hand to the wrist in ice water had no effect on the volume of the right hand. This observation was repeated six times, the left hand being warmed up till it felt hot to touch between each immersion. Application of ice to the patient's cheek also caused no change in hand volume.

On two other occasions similar results were obtained with the patient clothed, seated in a comfortable chair, and kept warm by blankets. Continuous immersion of one hand in ice water for two minutes, and intermittent immersion for 4½ minutes caused no change in the volume of the other hand, although the continued cold caused pain. Similarly, no change in hand volume occurred when the skin of the forearm was pricked with a pin. These experiments were done while the patient was being treated by the head-up bed regime, and her blood pressure seated was 120/80 mm. Control observations on normal people showed that immersion of one hand in ice water, or pricking the skin, regularly showed a sharp fall in the volume of the other hand.

Similarly, in Case 2, no change in hand, finger, or forearm volume or blood flow was caused by ice applied to the cheek or by ice water to the hand. Similar results were obtained during faradism to the skin sufficient to raise a wheal, and by a sudden, unexpected, loud noise. Case 3 also failed to show any response in fingers or forearm to these stimuli (Fig. 1).

It is therefore concluded that the disorder of blood pressure regulation present in these three cases is due to a similar failure of the normal mechanism responsible for causing reflex vasoconstriction in response to a fall in blood pressure.

The lesion is likely to be above the spinal reflex level, either in the afferent nerves or the central mechanism. A lesion of the afferent nerves is thought to be unlikely because no reflex response

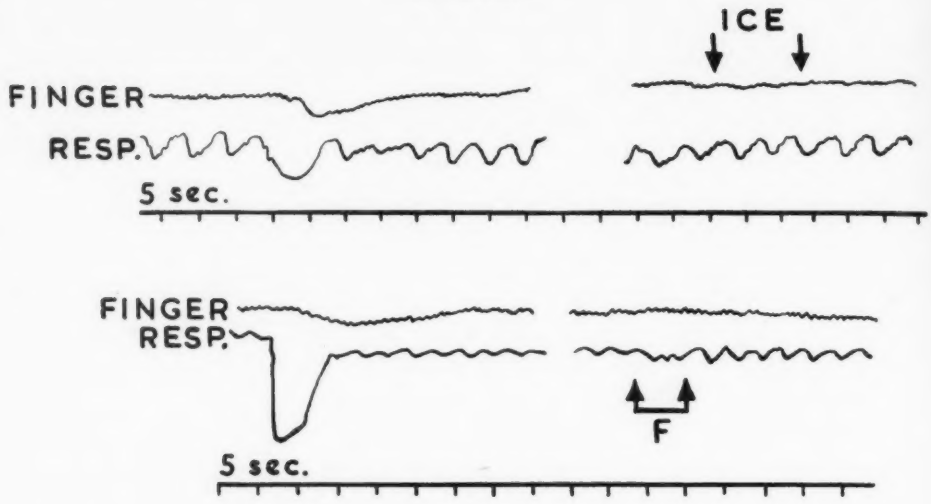

FIG. 1

Upper Record. CASE 2.—Normal response to deep inspiration, but no response to immersion of the other hand in ice water to the wrist. Plethysmograph temperature 35° C., room temperature 25° C., patient comfortably warm.

Lower Record. CASE 3.—Normal response to deep inspiration, but no response to faradism (F) sufficient to raise a wheal, and to make him "catch his breath." Plethysmograph temperature 35° C., room temperature 19·5° C, patient warm and comfortable.

was obtained from stimuli that were appreciated by the patient, and travelled by a variety of paths. A central lesion is therefore thought to be responsible.

Further localization by experiment has not been achieved, and the association of disturbances in the regulation of blood pressure, pulse rate, sweating, and sexual function which is found in this disease does not give any clear indication of the site likely to be affected. The disorder appears to be confined to the autonomic nervous system, and can show progression. Thus, in the first case reported, a fall in blood pressure at first caused a rise in pulse rate, while later the pulse became unchanging, and in a patient described by Ghrist and Brown (1928) anhidrosis was present on the right side for six years before becoming complete. The nature of the lesion, however, is quite obscure.

SUMMARY

Analysis of observations on three cases of postural hypotension provides strong evidence that the disorder is due to a central failure of the carotid reflex.

I wish to thank Dr. C. G. Baker and Mr. Harvey Jackson for access to Cases 2 and 3 respectively. Many of the observations on the first case are abstracted from a thesis for the M.D. degree submitted during an appointment as Assistant in the Department of Medicine in the University of Aberdeen.

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PERIPHERAL GANGRENE IN MYOCARDIAL INFARCTION

BY

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Peripheral gangrene caused by the extreme vaso-constriction that accompanies severe circulatory failure in such a disease as cholera is well recognized. Its occurrence, however, as a complication of myocardial infarction is such an uncommon event, to judge from the literature, that the reporting of two cases seems to be justified.

Case Reports

Case 1. The patient was a married man of 53, a hairdresser. For two years he had complained of retro-sternal and epigastric pain brought on by exertion and relieved by rest. Before this he had been in good health.

On December 24, 1948, he was seized with severe pain behind the sternum and in the epigastrium accompanied by shortness of breath and flatulence. His doctor made a diagnosis of coronary thrombosis and gave him morphine of which he received in all two and a half grains at home. His condition did not improve and he was admitted to hospital on December 28th.

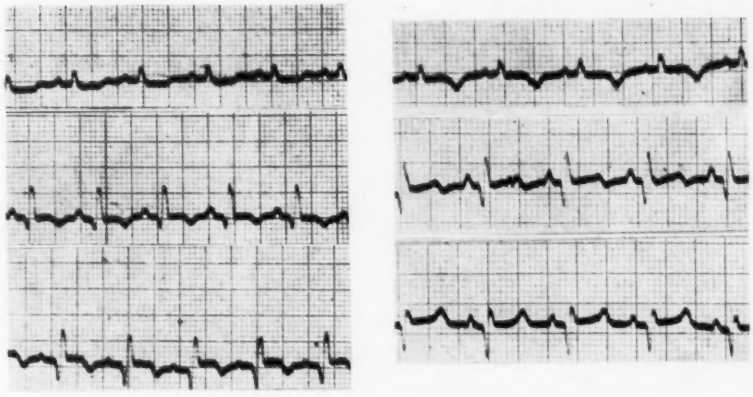
On admission he was severely dyspnœic at rest. There was no œdema. He was pale and it was noted that the end of his nose was blue and cold. The pulse was impalpable at the wrist and the blood pressure was 80/60. The apex rate was 100 a minute and the rhythm was regular. The heart showed no clinical enlargement and the heart sounds were normal. There was no pericardial friction. There were loud moist sounds all over both lungs, especially towards the bases. The liver was not enlarged.

He remained seriously ill with a heart rate of around 110 a minute until December 30th, when he seemed to be a little better, but it was found that the right foot had become cold and blue up to the level of the ankle, and was anæsthetic over the same area. No pulse could be felt at the ankle, though the femoral pulses were present on both sides. On this day also it was noted that the whole of the nose was blue, livid, cold and anæsthetic, and that there was a clear line of demarcation with the normal skin at the base of the nose. The tips of the ears and the tongue were unaffected, but there were some blotchy blue areas on the hands. The fingers were unaffected. Anti-coagulant treatment was started on this day.

On December 31st, the left foot became affected in exactly the same way, and the right foot remained blue, cold and anæsthetic. The prothrombin time was 36 seconds and a normal control was 25 seconds.

He remained gravely ill, and on January 3, 1949, a blood pressure reading of 60 mm. systolic with no diastolic end point was made: he died on this day. Electrocardiograms on the fourth and tenth day of the illness showed evidence of extensive myocardial infarction (Fig. 1).

Necropsy. There was gangrene of the nose with a well-defined line of demarcation, and small bullæ over the healthy skin at the junction. Both feet showed gangrene, with the skin black, swollen, and wrinkled (Fig. 2). The fingers and ears did not show gangrene.



A B

FIG. 1.—Case 1. Electrocardiograms. (Præcordial leads omitted.) (A) Fourth day of illness. (B) Tenth day of illness.

The pleural cavities contained an excess of blood-stained fluid. The lungs showed congestion and œdema of the bases with patches of bronchopneumonia. The pericardial cavity contained a slight excess of fluid.

The heart was of average size. There was no pericarditis. All the valves were healthy. There was a large area of recent infarction involving the anterior, lateral and posterior parts and also the inter-ventricular septum. There was widespread ante-mortem thrombosis adherent to the endocardium of the left ventricle (Fig. 3).

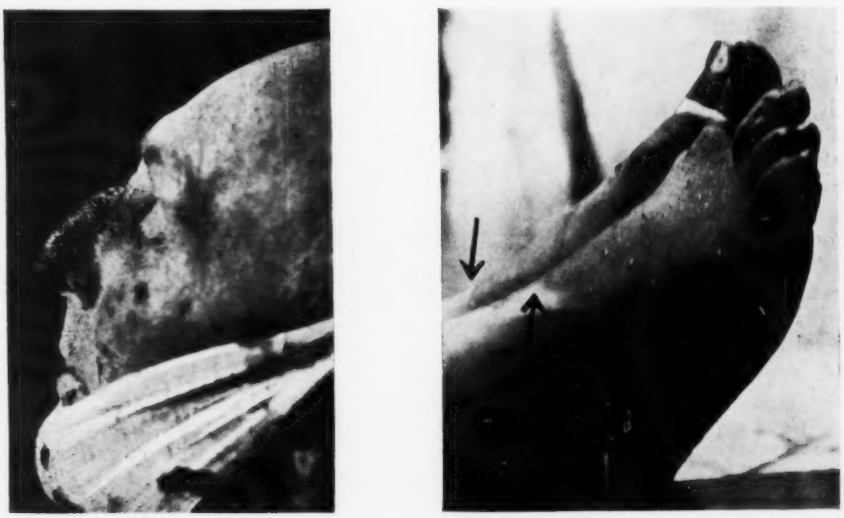


FIG. 2.—Case 1. After death, showing gangrene of the nose and feet. Arrow shows edge of gangrenous area.

FIG. 3.—Case 1. Left ventricle opened to show extensive recent infarction and ante-mortem intracardiac thrombosis.

The left coronary artery showed a recent thrombus completely occluding the lumen distal to the origin of the descending branch, which was itself completely obliterated by atheroma at its origin. The circumflex branch was greatly narrowed by atheromatous degeneration. In the right coronary artery there was a very recent thrombus completely occluding the lumen just proximal to the origin of the inferior interventricular branch.

The aorta was free from atheroma. The abdominal viscera showed passive venous congestion but no other naked-eye abnormality.

Dissection of the femoral, popliteal, peroneal, and posterior tibial arteries as far as the ankles and the dorsales pedis and lateral plantar arteries on both sides revealed no evidence of thrombosis or of embolism, and there was no naked-eye evidence of intimal degeneration in these vessels.

Case 2. A housewife of 63 had for 15 years been subject to attacks of numbness of the fingers when exposed to cold and stated that her toes were always cold. There was no history of any serious illness in the past.

Two months before the onset of her illness she had a short attack of faintness and rapid irregular heart action. A fortnight later there was another attack of palpitation associated with a tight feeling in the epigastrium. She went very pale and vomited. After this she noticed marked shortness of breath.

One day before admission, while in bed, a very severe pain developed in the centre of the upper

part of her chest radiating through to the back and into the shoulders and both sides of the neck. The pain was like a tight band round the chest. She became very short of breath, broke out into a sweat and went pale. The pain lasted, severely, for four hours and an ache remained for twenty-four hours.

She was admitted to Dryburn Hospital, Durham, on April 18, 1949. On admission she was noted to be very ill, very dyspnœic and slightly cyanosed. The heart rate was 102, regular with extrasystoles, and the blood pressure was 140/90. Obesity prevented accurate cardiometry, but the heart sounds were normal. Numerous rales were present in the chest, and the liver was palpable and tender. The jugular veins were distended.

The fingers and toes were blue and cold, but the rest of the hands and feet were warm. The radial and dorsales pedis pulses were palpable on both sides. Sensation was blunted over the tips of the digits but was normal elsewhere.

Progress. She became worse rapidly. On April 21 the tip of the nose was noted to be blue, and there was extension of the cyanosis of the fingers and toes.

An electrocardiogram on April 21 (Fig. 4) showed depression of the S–T period in lead I, biphasic T in lead II and deep Q with elevation of S–T in lead III. Chest leads not taken.

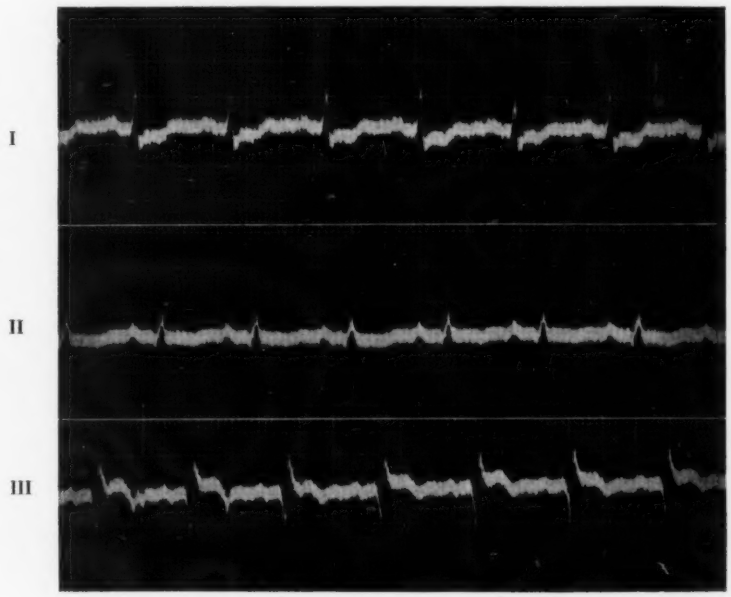


FIG. 4.—Case 2. Electrocardiogram on fourth day of illness.

A blood examination on April 20 showed E.S.R. 24 mm. in one hour, hæmoglobin 11·2 g., and white cells 11,000 per c.mm. The Wassermann reaction was negative. The urine contained albumen but no sugar.

Anti-coagulant treatment with heparin and dicoumarol was given between April 23 and May 5.

She was transferred to Newcastle General Hospital on May 13. The physical signs were the same, except that there was slight œdema of the ankles, but no cyanosis. The blood pressure was 125/85. There was no obvious enlargement of the heart, and the heart sounds were normal. There

were a few rales at the lung bases. There was right subcostal tenderness, but the liver could not be palpated.

There was a dry scab on the tip of the nose with a surrounding area of hyperæmia. The lobes of the ears and the tip of the tongue were normal. The index finger of the left hand was blue and cold, but there was no gangrene; the rest of the hand was normal and the radial pulse was palpable. There was dry gangrene of all the digits of the right hand, which extended well up onto the hypothenar eminence; the radial pulse was palpable. There was dry gangrene of all the toes except the right little toe. The dorsales pedis and posterior tibial pulses were palpable on both sides (Fig. 5).

An electrocardiogram showed depression of S–T in lead I, a flat T in lead II, and deep Q, elevated S–T, and inverted T in lead III. Chest leads showed a low voltage T from V4 to V6.

On July 5 there was persisting QIII, TIII pattern.

On December 7 lead I was now normal with persisting QIII, TIII pattern, but T waves in V4–6 now well upright.

Progress. Her general condition improved steadily with disappearance of the œdema and cyanosis in a few weeks. The gangrenous patch on the tip of the nose quickly separated leaving a smooth, slightly depressed scar. The toes separated slowly and fell off at the distal inter-phalangeal joints with good healing. The fingers of the right hand all separated with the exception of the thumb which is still adherent at the time of writing. A healing surface has been left in all areas. The patient is now ambulant, comfortable, and cheerful, eight months after the attack. Several episodes of pallor and cyanosis of the left hand have been observed during her long stay in hospital. Screen examination showed a transverse heart of normal size and shape.

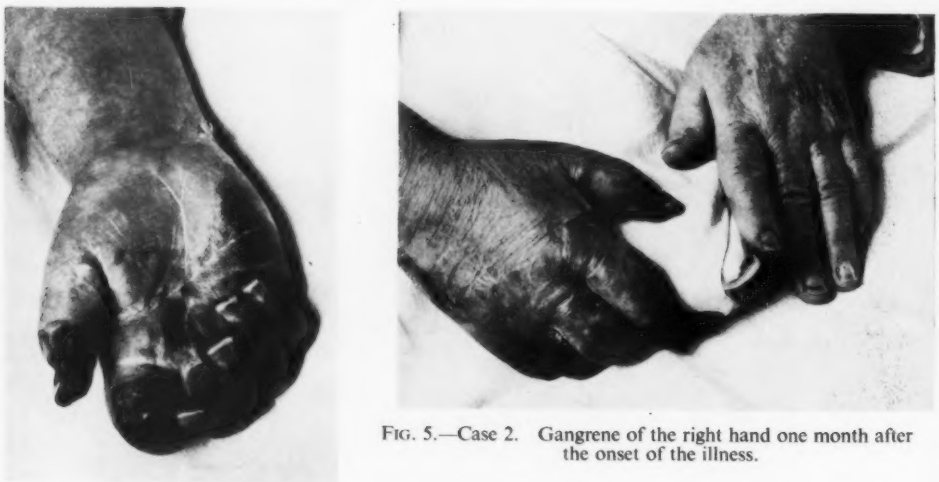


FIG. 5.—Case 2. Gangrene of the right hand one month after the onset of the illness.

DISCUSSION

The occurrence of peripheral gangrene in acute heart failure is an uncommon but recognized event. Perry and Davie (1939) report a case of hypertensive heart failure in a man of 64 in which both feet became gangrenous very shortly before death, and in which no obstruction of the iliac, femoral, or popliteal arteries could be demonstrated. Fishberg (1946) states that he has seen peripheral gangrene as a rare complication of myocardial infarction, and Abrahams (1948) describes incipient peripheral gangrene in a case of paroxysmal tachycardia.

A possible explanation of the phenomenon is advanced by Fishberg (1938) who observed the

co-existence of engorged jugular veins with collapsed veins in the extremities in cases of extreme failure of the right heart. He found by direct measurement that the jugular venous pressure might be as high as 20 cm. of water while at the same time the pressure in the antecubital vein was under 1 cm. With improvement, which was exceptional, the antecubital pressure rose to that in the jugular vein. The phenomenon was interpreted as a manifestation of vasoconstriction in the extremities, evoked probably reflexly by extreme diminution of cardiac output, in other words an analogue in heart failure of what was long ago demonstrated in experimental shock. The selective vasoconstriction is said to result in a redistribution of blood, a smaller portion of the cardiac output going to the limbs, and a larger portion to the brain and presumably to the other viscera. Symmetrical gangrene was observed twice. The writer suggests that the rare peripheral gangrene of heart failure is angiospastic in origin.

The gangrene of the legs in our Case 1 might reasonably be attributed to embolism, especially as there was intracardiac thrombosis, but a careful search of the arteries of the lower limbs failed to reveal such embolism, and this, coupled with the fact that there was gangrene of the end of the nose at a comparatively early state of the illness, leads us to conclude that intense vasoconstriction, following massive myocardial infarction, was the explanation of the gangrene in all the observed situations.

In Case 2 there was a history of attacks of Raynaud's disease before the myocardial infarction took place and this was confirmed by the observation of typical coldness, blanching, and cyanosis of the hands on several occasions afterwards. It is suggested that the very extreme degree of peripheral gangrene which occurred in this case, involving as it did the tip of the nose, the greater part of one hand and nine toes, was caused by an extreme degree of vasoconstriction following a myocardial infarction in a patient subject to Raynaud's disease.

Summary

Two cases are described in which gangrene of the nose and of the limbs followed a myocardial infarction. In one case, a subject of Raynaud's disease, recovery occurred after the loss of much tissue. It is suggested that the gangrene which may occur as a rare complication of severe heart failure is caused by intense and prolonged peripheral vasoconstriction.

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PAROXYSMAL NODAL TACHYCARDIA WITH RETROGRADE HEART BLOCK

BY

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Paroxysmal nodal tachycardia is not uncommon, and may be divided into three types, in which the rhythm arises in the upper, middle, or lower part of the A-V node. Low nodal tachycardia, which is characterized by an inverted P wave following the R wave at a constant interval, was found in 18 out of 253, and 8 out of 42 cases of paroxysmal tachycardia analysed by the electrocardiograph in the series reported by Hume (1930) and Campbell and Elliott (1939) respectively, i.e. in 9 per cent.

Lewis (1925) showed that in "low nodal" rhythm produced experimentally, depression of conduction, such as follows vagal stimulation, leads to gradual lengthening of the R–P interval until auricular beats may be missed. It is rare to find this phenomenon clinically, and the case of Drury (1924) appears to be the only report of retrograde heart block during a paroxysm of tachycardia. For this reason, the following case is recorded. Other points of interest were also found.

Case Report

The patient was a well-built girl of 11 years. Her past history was one of good health, apart from one illness which was probably her first attack. For this she was admitted to another hospital in February, 1949, with cough, nausea, and a regular pulse rate of 160 a minute. She had become unconscious a week before and this was probably the onset of the tachycardia. On admission she was not distressed; there was enlargement of the heart, and of the liver, but no congestion of the neck veins or œdema. Her tachycardia continued at the same rate until the fourth day in hospital, when the pulse rate gradually fell to 80 a minute. The heart returned to normal size within a few days. No electrocardiogram was taken during the tachycardia, but tracings were normal 11 and 24 days after it had stopped. It seems likely that this was her first paroxysm of tachycardia; it was certainly of 3 days and possibly of 10 days duration.

In April and May, 1949, when seen as an out-patient, she was well, and no abnormality was found in the heart, which was of normal size radiologically.

Present attack. On July 29, 1949, she complained of nausea, anorexia, and dizziness for no apparent cause, but was not conscious then, or at any time, of palpitation. She remained at home, but not in bed, and her symptoms continued. On August 4, she vomited once, and her doctor found a very rapid regular pulse rate, and sent her to hospital that day. On admission she was of healthy appearance and colour, and not distressed on lying flat, though she had some dyspnœa on effort. There was no venous congestion or œdema, and the liver could not be felt. The pulse was regular at about 200 a minute, and a corresponding pulsation was seen in the neck. The heart was enlarged, the apex beat being just beyond the mid-clavicular line in the fifth intercostal space. The heart sounds were normal and there were no murmurs. B.P. 100/80. No other abnormality was found. The pulse rate was not influenced by holding the breath, by changes of posture, or by pressure on either carotid sinus or on the eyeballs. These manœuvres had no effect clinically on any occasion.

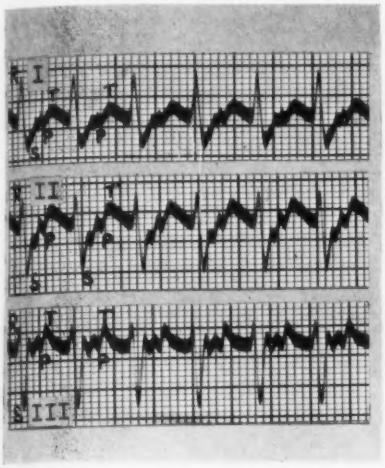


FIG. 1

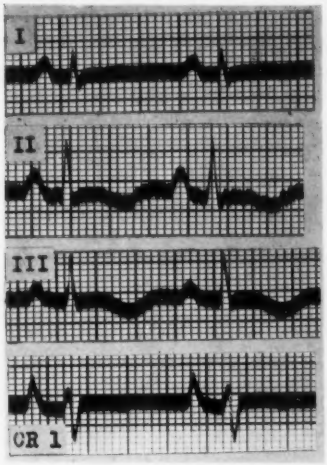


FIG. 2

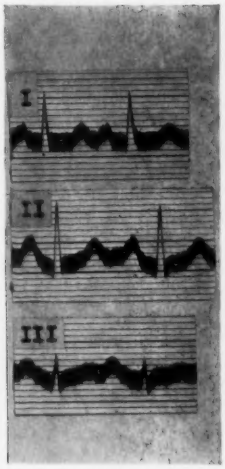


FIG. 3

FIG. 1.—4/8/49. Regular nodal tachycardia, rate 195 a minute. QRS duration 0·12 sec. R–P interval 0·14 sec.
FIG. 2.—9/8/49. Sinus rhythm, rate 75 a minute. P waves are all upright, but T is flat or inverted in all and is broadened.
FIG. 3.—9/9/49. Sinus rhythm, rate 100 a minute. T waves now upright in all leads.

There was a regular tachycardia, rate 195 a minute. P waves appeared to follow the ventricular complexes, and were inverted in leads II and III; the R–P interval was 0·14 sec.; and the ventricular complexes were slightly abnormal in form and were of 0·12 sec. duration (Fig. 1).

Carotid sinus pressure had no effect, but pressure on the eyeballs, while not changing the ventricular rate, produced progressive lengthening of the R–P intervals, and one auricular beat was missed (Fig. 4).

The patient was then given a trial dose of 3 grains of quinidine sulphate by mouth. On the following day (August 5) her tachycardia continued, with no change in the clinical findings, and she was comfortable apart from the anorexia and some nausea. A teleradiogram (Fig. 7A) showed generalized enlargement of the heart with a cardiothoracic ratio of 57. There was no change in the limb leads, apart from a drop in the pulse rate to 178 a minute. Lead CR I showed pointed upright P waves following the R waves at a constant interval of 0·14 sec. (Fig. 5). Quinidine sulphate was given by mouth in divided doses, 8 grains on the 5th, 15 grains on the 6th, and 20 grains on August 7 and 8.

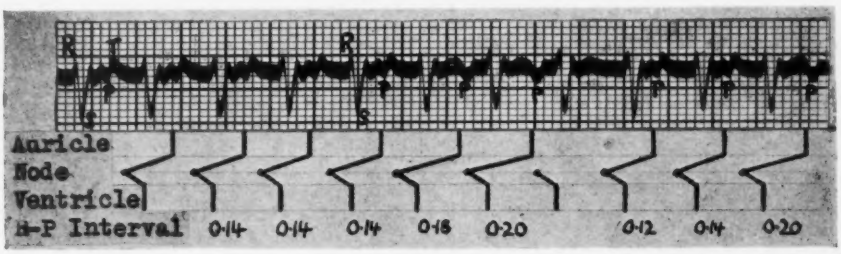


FIG. 4.—4/8/49. Lead III. Pressure on eyeballs commencing about 15 sec. before this tracing was taken produces block of retrograde spread of impulse to auricles without influencing ventricular rate. Probable mechanism is indicated. R–P interval is prolonged and one auricular contraction is missed.

On August 8, there was still no clinical change; the ventricular rate was 158 a minute in the limb leads, but was 170 a minute in the chest leads taken a few minutes later (Fig. 6). P waves were unchanged in form, but occurred irregularly at a slower rate than the R waves. In the strip of lead III seen here, 3: 2 V-A block is constant, and in leads I and II a similar block predominates. In lead CR 1 the mechanism of a 3: 2 retrograde block is tentatively illustrated, although it is possible that complete V-A dissociation had now arisen, as the auricular rate was nearly regular at 105 a minute, and the ventricular rate had accelerated a little. About 12 hours after these tracings were taken, the pulse was found to have slowed to less than 100 a minute, though the patient had noticed no change in her heart rate.

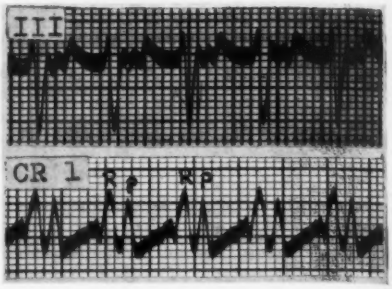


FIG. 5.—5/8/49. Limb leads as on previous day, but rate is now 178 a minute. Lead CR 1 shows R wave followed by P wave; compare with form of P and R in lead CR 1 in Fig. 6.

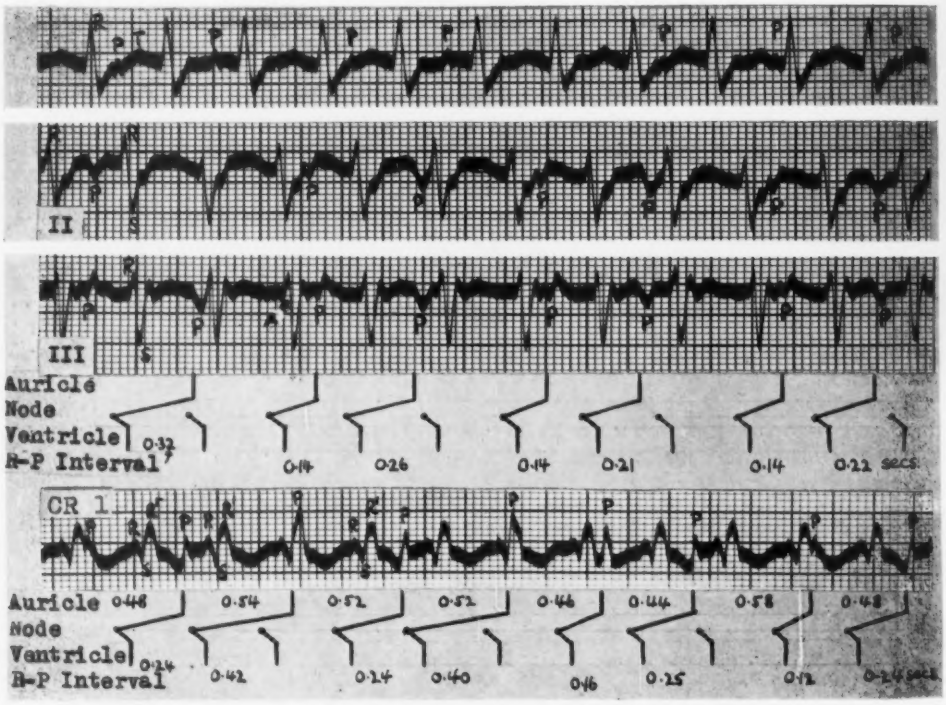


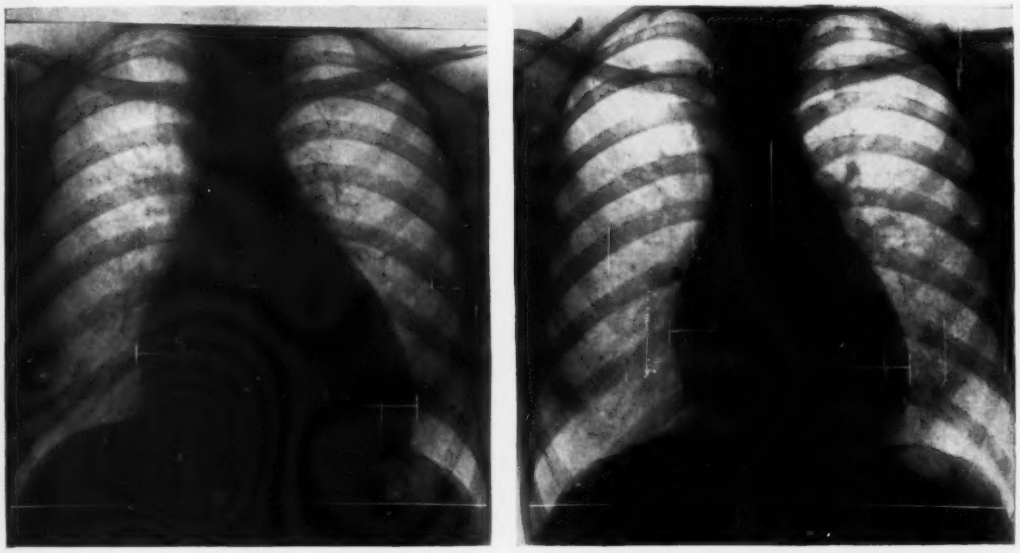
FIG. 6.—8/8/49. Regular ventricular tachycardia continues, rate 158 a minute in limb leads, 170 a minute in lead CR 1. P waves now occur at a slower rate than R waves and 3: 2 V-A block is seen in lead III and during most of leads I and II. A similar mechanism is suggested for leads CR 1. Note double R wave is now more obvious in CR 1. QRS duration in all is 0·14 sec.

On the next day (August 9) the pulse was regular at 80 a minute; the patient felt better and had regained her appetite. Quinidine was stopped. There was regular sinus rhythm, rate 75 a minute,

with inversion and broadening of T in leads II and III, as well as in leads CR 3 and 6, which are not shown here (Fig. 2). The time of electrical systole was prolonged by Bazett's formula, Q–T in lead II being 0·44 sec. for a cycle of 0·74 sec. This gives a value for factor K of 0·51.

The patient was well subsequently, and normal rhythm was maintained. On the fourth day after return to normal, a teleradiogram (Fig. 7B) showed a normal heart size, with a cardiothoracic ratio of 49 per cent. On the following day the patient was discharged home.

When seen a month later, she was well, with a heart that appeared normal, and a sinus tachycardia of 100 a minute, slowing on carotid pressure, and with all T waves upright (Fig. 3).



A B

FIG. 7.—(A) 5/8/49. Generalized enlargement of the heart on the eighth day of tachycardia. Cardiothoracic ratio 57. (B) 12/8/49. Normal sized heart on the fourth day after return to normal rhythm. Cardiothoracic ratio 49 per cent.

Diagnosis. Low nodal tachycardia was diagnosed, as there was undoubted retrograde activation of the auricles, and vagal stimulation (Fig. 4) delayed this retrograde conduction in the way described by Lewis (1925). However, the ventricular complexes were not identical with those found afterwards, being slightly prolonged and deformed during the paroxysm. This difference was clearest when leads CR 1 were compared. Ventricular paroxysmal tachycardia could not be diagnosed, as, in that condition, when P waves are seen, they occur at a slower rate and independently of the ventricles. Some degree of intra-ventricular block must therefore have occurred during the paroxysm.

DISCUSSION

Retrograde heart block in nodal rhythm was first demonstrated by Lewis (1914); he found that vagal stimulation prolonged the R–P interval when this was seen in nodal rhythm that had been set up experimentally in dogs. Later, Lewis, White, and Meakins (1914) investigated in the cat the effect of asphyxia on nodal rhythm caused by cooling the S-A node. In 3 or 4 minutes of asphyxia, there was progressive lengthening of the R–P interval and finally 2: 1 retrograde block of the

auricle: they concluded that the part of the conducting system most susceptible to block lay at a higher level (i.e. nearer the auricle) than the actual seat of impulse discharge in the A-V node.

Clinical examples of similar block in nodal rhythm were given by White (1915) and by Gallavardin and Gravier (1921): in their cases the ventricular rate was of the order of 40–60 a minute, and vagal stimulation produced not only a marked slowing of the ventricle, but also a lengthening of the R–P interval; on one occasion, after digitalis, White found an R–P interval of 0·42 sec., which may be compared with that postulated in some beats in Fig. 6.

Drury (1924) described short paroxysms of nodal tachycardia occurring terminally in a man with infective endocarditis. In certain of his tracings he found progressive lengthening of the R–P interval; after this had reached about 0·14 sec., either an auricular beat was dropped or the impulse from the last auricular beat re-entered the ventricle and gave rise to a premature beat, i.e. reciprocal rhythm; this was found also by White, and by Gallavardin and Gravier, but was not seen in this case.

It is difficult to determine whether the retrograde block found on the last day of this paroxysm was induced by quinidine or not. In view of Drury's case (when no drug was given) and of the fact that reversion to normal rhythm occurred here shortly after retrograde block was found, it seems most likely that the block developed as a result of fatigue in the conducting system towards the end of a long paroxysm of tachycardia.

The duration of this paroxysm was probably ten days, but in neither attack was the patient conscious of the start or the finish of the tachycardia. Gradual slowing of the heart rate, from 195 to 158 a minute is unusual, as paroxysmal tachycardia has a typically constant rate in any one attack, although an individual may have different paroxysms at different rates (Campbell and Elliott, 1939). It seems unlikely that it was due to the quinidine given. A similar slowing, from 173 to 124 a minute in a seven-day paroxysm was described by Marvin (1923).

Cardiac dilatation was found during both paroxysms in this patient. On the 8th day of this one, the cardiothoracic ratio was 0·57, instead of 0·45 and 0·49 on teleradiograms taken in May and September respectively.

Inversion and prolongation of T waves was seen in leads II, III, and CR 3 and 6 on the day after the paroxysm had stopped, but unfortunately the recession in these changes was not followed. Inversion of T following paroxysmal tachycardia is well recognized (Campbell, 1942; Zimmerman, 1944), and the T wave may be prolonged as well as inverted (Cossio *et al.*, 1944; Ward, 1946), which change appears to be independent of the use of quinidine. In several illustrations in articles on this subject it will be seen that electrical systole (QT) is thus prolonged after a paroxysm of tachycardia. Using the formula of Bazett (1920) electrical systole was considerably prolonged, K being 0·51 in Fig. 2 instead of the normal 0·37 to 0·40. This may have been due to residual cardiac dilatation after the paroxysm.

Summary

A case of low nodal paroxysmal tachycardia is described, occurring in a girl of 11 years with an apparently normal heart. The paroxysm lasted probably ten days, and for the last four days the patient was treated with quinidine by mouth.

Reflex vagal stimulation on the seventh day of the tachycardia delayed retrograde conduction, prolonging the R–P interval progressively and causing an auricular beat to be dropped.

About 12 hours before the tachycardia stopped, spontaneous retrograde block was found to have developed, with predominantly 3: 2 V-A rhythm.

During the period of observation the ventricular rate gradually slowed from 195 to 158 a minute.

Cardiac dilatation was found during the tachycardia, but the heart had returned to normal size on the fourth day after the paroxysm stopped.

Temporary inversion and broadening of T waves was seen after the attack, causing lengthening of the time of electrical systole.

My thanks are due to Dr. D. H. Davies for permission to publish this case and to him and Professor Bruce Perry for their helpful criticism.

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FLUORESCEIN TEST OF CIRCULATION TIME IN PERIPHERAL VASCULAR DISEASE

BY

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There are already many well-established techniques and tests used in the diagnosis of occlusive arterial disease and in evaluating the degree of severity of a given case and the response to therapeutic procedures. A reliable objective measurement of the speed of the blood flow to the extremities would, however, provide additional useful information in the study of peripheral vascular disease, but there has not yet been available a simple test that measures the speed of flow to the periphery of a limb.

Tests of circulation time fall into two main groups—the subjective, which require the co-operation of the patient, and the objective, which are independent of his reactions and of his collaboration. Much American work has been based on a subjective test (Spier, Wright and Saylor, 1936) in which the intravenous injection of a solution of magnesium, calcium, sodium, and copper salts gives to the subject a sensation of warmth in the throat, hands, perinæum, and feet as the solution reaches those areas. Histamine or sodium cyanide have been used to give objective end points, but they are unpleasant for the patient and give only a limited amount of information. We have used radioactive sodium (Na_{24}) to assess arterial circulation times and to study tissue build-up curves, (Quimby, 1947 ; Elkin *et al.*, 1948) but have found that the method involves technical and administrative difficulties that outweigh its usefulness, although venous circulation times can be readily and accurately measured with the method (Wright, Osborne, and Edmonds, 1948).

In 1942, Lange and Boyd introduced fluorescein as a test substance; it has the great advantage that it is non toxic, not unpleasant for the patient, and can be detected in very high dilution when the patient's skin and mucous membranes are observed under ultra-violet light. The test as originally introduced enables one to detect, in a given area, the presence of circulating blood containing fluorescein, and an estimate can be made of the time taken for the blood flow between the point of injection and any other chosen part of the skin. The end-point by this method is not sharp, but Nathanson and Merliss (1943) modified the test so that by the use of intradermal histamine wheals the end-point is made to be precise and clear.

We have found the test thus modified to be extremely simple and reliable—a convenient index of peripheral blood flow and of the response to therapeutic procedures. It is, of course, affected by conditions such as heart failure, myxœdema, and hyperthyroidism, but in their absence it gives information about the integrity of the peripheral vessels. It is essentially a measure of the speed of flow to the skin in a chosen area, and as such is influenced by those factors that affect skin flow, the most important of which is skin temperature.

Plethysmography measures more accurately the volume of flow to the limb, and therefore principally to its muscles, but is less readily adaptable to constant routine use and is subject to technical difficulty and error. A test of circulation time can never replace plethysmography but we find that it is a useful index in the routine management of patients with peripheral vascular disease.

Lange and Boyd (1944) studied patients with peripheral vascular disease and showed how the method can be used to demarcate areas of incipient gangrene. The test has been found to be useful in the investigation of patients with heart failure (Winsor, Adolph, Ralston and Leiby, 1947) and particularly in congenital heart disease in children (Gasul, Marino and Christian, 1949); and in estimating the blood flow in the pedicled skin flaps and tubes used in plastic surgery (Hynes and Macgregor, 1949).

Technique

Observations made on patients with peripheral vascular disease are notoriously subject to variation due to environmental conditions, and Winsor *et al.* (1947) have shown the effect on the fluorescein circulation test of different environmental temperatures. Past work has suffered through the lack of a recognized standard technique. To be of value the results in patients must be obtained in circumstances that are as standardized and constant as possible.

Our practice is to carry out the test in a room which can be darkened and in as warm an atmospere as is practicable, so that vasodilatation and relaxation of the vessels of the limbs is induced. The patient lies on a couch in a warm room and skin temperature readings are taken of the soles of the feet. Both the patient's arms are then immersed in arm baths containing hot water, about 42° or 43° C., for over ten minutes, so that considerable body sweating is induced. Oscillometric observations are made on the patient's calves, and at the conclusion of the ten minutes the skin temperatures are again taken and thereby additional information is gained about the capacity of the vessels to dilate.

Small intradermal wheals are then made with injections of 0·05 ml. of a mixture of equal parts of 5 per cent. procaine and 1 : 1000 histamine acid phosphate. The wheals can be placed on any part of the skin to which it is desired to measure the speed of circulation. When investigating the flow to the lower limbs, we produce wheals just above each patella, on the dorsum of each foot just proximal to the base of the middle toe, and at the elbow just beside the antecubital fossa of the left arm.

4 ml. of a 20 per cent. solution of sodium fluorescein is then rapidly injected intravenously at the right elbow, the injection being carried out in the dark under the light of a " Mercra " 125-watt M.B.W./V ultra-violet lamp which has been appropriately filtered in its manufacture so that the radiation emitted is in the range 3130A to 4070A, with 95 per cent. of the radiation concentrated at 3650A. This is the appropriate lamp to use as the fluorescence of fluorescein is maximal at a wave-length of 3600A.

The time is measured with a stopwatch from the beginning of the injection until the first appearance of fluorescence in the intradermal histamine wheals previously placed as markers. The end-point is clear and sharp, and the appearance of the wheals during the test has been likened to the sudden illumination of a small light. The wheals fluoresce with a bright yellow-green fluorescence which contrasts sharply with the initial blue-purple appearance of the surrounding skin. Generalized skin fluorescence can then be observed and its distribution noted. The first appearance of fluorescence in a very ischæmic area takes the form of a green halo surrounding the histamine wheal, the wheal itself remaining as a dark central area. The usual appearance, however, is immediate bright fluorescence of the whole wheal, a fluorescence that extends along the pseudopodial extensions of the wheal.

The following measurements are made: the time is taken from the beginning of the injection until the first appearance of fluorescence in the wheal at the antecubital fossa of the left arm. This represents the time taken for blood to travel from the right to the left arm, and is termed the arm-time. Similarly the time is measured until fluorescence appears in the wheals at the knees (knee-time) and on the dorsa of the feet (foot-time). The difference between the foot and arm times is called the foot-minus-arm-time, and is the most useful index as it eliminates the variables of the pulmonary circulation, and measures the speed of flow in the arterial segments of the lower half of the body.

The patient is warned that he will have a slightly yellow appearance for a few hours and that his urine will be discoloured. In agreement with other observers, we have found that about 4 per cent. of patients experience a transient feeling of nausea after the injection. None have been sick, and the drug appears to have no adverse effect whatsoever on the great majority of subjects. Most patients evince considerable interest in the whole procedure, and many patients willingly subject themselves to frequent observations.

Results

Normals. The test was performed on fifteen adult persons who were either healthy volunteers or surgical cases with normal vascular systems. In no case was there any evidence of cardiac or peripheral vascular or endocrine disease.

The results are tabulated in Table I, and compared with the normal results published by Winsor *et al.* (1947), who were principally concerned with the use of the test in patients with congestive cardiac failure. There is a fairly wide range of normal arm-times and foot-times, but we regard a foot-minus-arm-time (i.e. a foot-time minus arm-time) in excess of 13 seconds as being indicative of some cause of circulatory slowing, when the test is performed under standard conditions. In a normal circulation the times to the two feet should be identical.

TABLE I

Fluorescein Circulation Times in 15 Normal Adults under Controlled Conditions

	Arm-time (sec.) A	Feet-time (sec.) F	Feet-minus-arm-time (sec.) F–A
Range	9–25	21–35	8–13
Mean	16·6	27·2	10·6
Standard deviation	±4·14	±4·06	±1.60
Standard error	±1·07	±1·05	±0·41
Winsor et al. (1947)			
Range	15–25	25–35	9–14
Mean	18·6	28·1	9·5

Thyrotoxicosis, Myxœdema, Heart failure, and Coarctation of the Aorta. Table II summarizes typical findings in various conditions. All times are accelerated in thyrotoxicosis, which is well illustrated in Case 16, a young woman of 27 with primary thyrotoxicosis. Her circulation times are both rapid, and the acceleration in the foot-minus-arm-time is statistically significant. Conversely, there is a slowing in myxœdema, and where the slowing is from a generalized cause such as myxœdema or heart failure, it is more apparent in the foot-times than in the arm-times, and so is reflected in prolonged foot-minus-arm-times. This is illustrated by Cases 17 and 18 where initially prolonged times were reduced to the normal range after adequate treatment with thyroid.

Times are prolonged in congestive failure, as shown by Winsor *et al.* (1947), and by Cases 19 and 20. Case 20 was an elderly patient of 68 with congestive heart failure and gangrenous charges in his right foot due to diabetes, changes that were reflected in the more prolonged times to his right foot. Case 21, with coarctation of the aorta, showed normal arm-times with very prolonged foot-times, a finding that is due to the longer course the blood to the lower half of the body has to travel through the collateral channels. Case 22 is interesting, a patient of 42 with thyrotoxicosis who had the right leg amputated for thromboangiitis obliterans five years previously; his arm-time was in the low normal range, and his left foot-time was also in the normal range; his foot-minus-arm-time was prolonged to 15 seconds, a significant prolongation due to the presence of occlusive arterial disease in his remaining leg.

TABLE II

FLUORESCEIN CIRCULATION TIMES IN MISCELLANEOUS CONDITIONS

Case No.	Arm-time (sec.) A	Feet-time (sec.) F	Feet-minus-arm-time (sec.) F–A	Remarks
16	12	17	5	Thyrotoxicosis.
17	15 14	64 27	49 13	Myxœdema. Before treatment. After one month's treatment with thyroid.
18	21 17	39 27	18 10	Myxœdema. Before treatment. After 10 weeks' treatment with thyroid.
19	24	52	28	Congestive failure.
20	34	69 (right) 41 (left)	35 17	Congestive failure. Diabetes. Gangrenous changes in right foot.
21	17	43	26	Coarctation of aorta.
22	12	27	15	Thyrotoxicosis. Left leg only, right having been amputated for thromboangiitis obliterans.

Peripheral Vascular Disease. The test has been applied to patients with peripheral vascular disease, and the summarized results are presented in Table III. The patients, in whom the presenting symptom was usually intermittent claudication, had clinical evidence of occlusive arterial disease, with poor arterial pulsations, delayed reactive hyperæmia and impaired oscillometric readings.

TABLE III

FLUORESCEIN CIRCULATION TIMES IN 30 PATIENTS WITH OCCLUSIVE ARTERIAL DISEASE

	Arm-time (sec.) A	Feet-time (sec.) F	Feet-minus-arm-time (sec.) F–A
Range	11–30	19–87	9–57
Mean	17·1	38·8	21·7
Standard Deviation	±5·00	±13·93	±10·84
Standard error	±0·91	±1·84	±1·43
Standard error of difference between mean and mean of controls	1·40	2·12	1·49

The group consists of 30 patients, with a total of 57 legs, 3 having previously been amputated because of vascular disease. The mean arm-time corresponds closely with the time observed in the control series, but there is a prolongation in the mean foot-time, which is statistically significant, and also in the foot-minus-arm-time, which is highly significant. Five patients of the group (17%) had normal foot- and foot-minus-arm-times, despite the unequivocal presence of occlusive arterial disease, an observation also noted by Kvale and Allen (1939). In two of these, however, the times to the two feet were unequal, a finding inconsistent with a normal circulation, as the objective demonstration of a difference in the foot-times is by itself evidence of arterial disease. Five other patients had normal foot- and foot-minus-arm-times to one limb, with prolongation to the other; in each case the prolongation was in the limb in which there were symptoms, and in which there was most objective evidence of disease. The criterion of normality for the purpose of these observations was taken as a foot-minus-arm-time of 13 seconds or less.

TABLE IV

FLUORESCEIN CIRCULATION TIMES IN PATIENTS WITH THROMBOPHLEBITIS MIGRANS

Case No.	Arm-time (sec.) A	Feet-time (sec.) F	Feet-minus-arm-time (sec.) F–A
53	18	36	18
	—	32	14
54	14	31	17
	—	24	10
55	17	41	24
	—	38	21
56	13	29	16
	—	30	17
Range	13–18	24–41	10–24
Mean	15·5	32·6	17·1
Standard deviation	±2·39	±5·55	±4·34
Standard error	±1·19	±1·96	±1·54
Standard error of difference between mean and mean of controls	1·6	2·22	1·56

We have not included knee-times in any of the tables. This is a less useful measurement, and even where there is considerable disparity in the times to the feet, the knee-times are usually almost identical on the two sides. Only in the presence of fairly gross femoral artery disease is there a relative slowing of the knee-times on that side.

The test has also been applied to four patients each of whom had presented with the clinical picture of transient and shifting thrombophlebitis, and in no case was there any clinical evidence of arterial involvement (Table IV). The results show a prolongation of the mean foot-times to an average of 33 seconds. This is barely significant in this small group. The foot-minus-arm-times, however, were prolonged to a mean value of 17 seconds, which is statistically significant. It is of interest that the foot-minus-arm time of this group of 4 patients was only below the level of 13 seconds in one of the eight limbs concerned. Case 53 has since he was first tested, recently developed intermittent claudication affecting the right calf, a symptom accompanied by the objective demonstration of more prolonged circulation times on that side.

EFFECTS OF THERAPY

Table V lists the results of a series of observations on the immediate effects of various forms of therapy on a man of 45 with thromboangiitis obliterans. His symptoms were, at first, chiefly in the right leg, although there was objective evidence of a poor flow in both feet. In the initial control observations there was a reasonable degree of agreement in the times, and a feature was the constant difference of 6–9 seconds between the circulation times to his two feet. Observations were made on two occasions following the intravenous injection of tetra-ethyl ammonium bromide (*TEAB*). The only effect was a slight prolongation of all times, due to the fall in blood pressure. This left the foot-minus-arm-times, and the difference between times to the two feet unaltered. The oral administration of 100 mg. of nicotinic acid and the intravenous injection of 1 grain of papaverine hydrochloride had no appreciable effect on the times (not tabulated).

The test was carried out one hour after the intravenous infusion of 200 ml. of 3 per cent. saline. This resulted, in this patient, in an acceleration of all his times, but left the difference between the times to his feet constant. When the test was performed 24 hours after right procaine paravertebral block, the difference between his foot-times was reduced to only 3 seconds, and following right

TABLE V

EFFECT OF THERAPY ON FLUORESCEIN CIRCULATION TIMES IN THROMBOANGIITIS OBLITERANS

Observation	Right Foot-arm time. F1 (sec.)	Left Foot-arm time. F2 (sec.)	Foot difference F1–F2 (sec.)
Control. 1	17	10	7
2	18	9	9
3	16	10	6
4	15	9	6
Tetra-ethyl ammonium bromide—			
200 mg.	17	8	9
250 mg.	18	8	10
200 ml. 3 per cent. saline I.V.	10	4	6
Right procaine paravertebral block	15	12	3
Right lumbar sympathectomy (time post-op.)—			
7 days	8	12	−4
10 days	10	13	−3
5 weeks	8	12	−4
5 months	9	9	0
9 months	13	20	−7
19 months	15	16	−1

lumbar sympathectomy all post-operative observations showed the difference between his feet-times to be reversed, the circulation time to the foot on the sympathectomized side being quicker than that to the other foot. The most recent observations showed a further increase in the times to the left, untreated foot, an increase that accompanied the first onset of symptoms referable to that foot.

Effect of lumbar sympathectomy.—The test has been carried out before and one week after lumbar sympathectomy had been performed on a series of patients with occlusive arterial disease. In every case an absolute acceleration occurred to the foot on the sympathectomized side. We have found that a useful index of the result of the operation is the degree of acceleration that results relative to the time to the foot on the untreated side. Usually, before operation the foot-time on the treated side has been longer than that to the untreated side, whereas after operation the time has been shorter. We have termed the resulting acceleration the relative acceleration, and in a series of 13 operations the mean relative acceleration was 17 seconds. Table VI summarizes these results.

This acceleration is fairly permanent, and the resulting quicker time to the foot persists over periods of months or years, although further organic change may occur in the vessels and alter the absolute time to the two feet. A small series of cases has been tested up to 3 years after operation and, although the times before are not known, where the time to one foot is quicker than that to the other, the quicker time has generally been on the side previously sympathectomized.

This acceleration is undoubtedly related to the rise of skin temperature that results on the treated side, a rise that is persistent and may last many years.

THE RELATIONSHIP OF SKIN TEMPERATURE TO CIRCULATION RATE

As we have pointed out, the observers who have used this test have often failed to standardize the conditions under which readings were made. Full dilatation of the peripheral vessels is essential if observations made on different occasions are to be strictly comparable. It is true that somewhat similar information can be obtained by taking readings of skin temperature but this is a technique much better adapted to detect changes occurring during a short space of time.

We carried out observations on a patient who had had a sympathectomy performed on a leg for chronic œdema which had disappeared after the operation and in whom the arterial circulation

TABLE VI

EFFECT OF LUMBAR SYMPATHECTOMY ON FLUORESCEIN CIRCULATION TIMES

Case No.	Observation	Treated Side Foot-arm time. F1 (sec.)	Untreated Side Foot-arm time. F2 (sec.)	Foot difference F2—F2	Acceleration on treated side relative to untreated side. (sec.)
23	Before	25	24	1	21
	After	12	32	−20	
24	Before	46	24	22	50
	After	4	32	−28	
25	Before	18	21	−3	17
	After	11	31	−20	
26	Before	14	9	5	11
	After	11	17	−6	
28	Before	15	12	3	8
	After	11	16	−5	
29	Before	21	21	0	7
	After	10	17	−7	
35	Before	18	11	7	10
	After	10	13	−3	
36	Before	21	12	9	20
	After	10	21	−11	
39	Before	38	20	18	17
	After	16	15	1	
41 (1st side)	Before	48	8	40	41
	After	14	15	−1	
(2nd side)	Before	15	14	1	9
	After	8	16	−8	
52	Before	9	9	0	1
	After	5	6	−1	
62	Before	13	13	0	13
	After	6	19	−13	
		Mean relative acceleration.			17·3

NOTES

(1) Cases 24, 35, 41, and 62 were patients with thromboangiitis obliterans ; remainder were arteriosclerotic.
(2) All observations after operation were made 5–7 days after.

appeared to be intact. After vasodilatation produced reflexly the circulation time to the sympathectomized side was much more rapid. This was still true after immersion of both limbs in water at 37°, but at 44°, when local heat had effected full vasodilatation on both sides, the times were equal as would have been anticipated. We conclude that the test gives information about the degree of vasodilatation that can be obtained by physiological means and is specially suitable for assessing the effect of therapeutic procedures.

Pickering (1933) noted that as a rule a limb affected by structural vascular disease was cooler than its fellow ; occasionally, however, the limb with the greater evidence of vascular disease was the warmer, and he suggested that the explanation of this anomaly was probably that in such warm limbs the circulation was maintained by the opening of collateral channels lying particularly in the skin or subcutaneous tissues. Such an explanation would also apply to those few cases in which we found that the fluorescein circulation times were normal in the presence of occlusive arterial disease.

DISCUSSION

The normal ranges and times quoted by Winsor *et al.* (1947) are included in Table I, and are of the same order as found in our control series. Kvale and Allen (1939) quote rather longer normal average foot-times than we have found with this technique, but this is because their method, that of Spier *et al.* (1936), was essentially a subjective one and the figures include the appreciable delay between the time when the test substance reached the patient's foot and his expression of

his sensation. Similarly, the normal times published for the fluorescein test by Kramer and Abramson (1947) were more prolonged, but were obtained without the assistance of the histamine wheal markers and are therefore unreliable.

The circulation times obtained in patients with occlusive arterial disease are, as one would expect, prolonged, and the vast majority of patients with arterial disease have different times to the two feet.

We feel that the fluorescein test of circulation time, because of its simplicity and objectivity, is worthy of more general use with a standard technique. It certainly provides an objective index of the severity of affection in the majority of cases, and serial observations over a period of years will provide interesting information regarding the development of impaired blood flow in the presence of occlusive arterial disease. We have shown that in cases of thrombophlebitis migrans, in which there is no evidence of arterial disease, there is already a significant prolongation in the difference between foot-time and arm-time. Prolonged times under controlled conditions are significant but normal times do not exclude impaired blood flow in a small minority of patients. The fact that it is possible to obtain normal circulation times when there is undoubted occlusive disease present makes the test less valuable as an absolute diagnostic agent, but all tests used in peripheral vascular disease suffer from the same defect.

In our series of sympathectomized patients, all of whom had evidence of occlusive arterial disease, there has been constantly an acceleration in the speed of flow to the foot on the sympathectomized side, and this acceleration has persisted in those patients who have been repeatedly examined, or have been examined for the first time some months or years after sympathectomy. Objective demonstration of an accelerated blood flow to the sympathectomized limb has been found to be of considerable value in reassuring the patient regarding the result of his operation, and the test provides a useful objective measurement of the effect of lumbar sympathectomy. Its value in measuring the degree of response to other therapeutic procedures designed to increase the flow of blood to the limbs is being further assessed.

Summary

The time taken for fluorescence to appear in small histamine wheals examined under ultra-violet light has been used as a measure of circulation rate.

The test may be used to study either general conditions in which the circulation rate is affected, such as heart failure and myxœdema, or to investigate peripheral vascular anomalies.

The average normal arm-time in a series of patients was found to be 16·6 seconds, and the average foot-time, 27 seconds. Significant prolongation of all times was usually found in myxœdema and heart failure, and all times were accelerated in hyperthyroidism. The foot-minus-arm-times reflect mainly changes in the peripheral vessels, and figures in excess of 13 seconds were usually due to the presence of occlusive arterial disease, especially when the arm-times were normal. Different circulation times to the two feet were indicative of an abnormal circulation even though the absolute times might be normal. In a minority of cases arterial disease existed when the circulation times were normal.

The test has been used as an objective index of the response to treatment. An average acceleration of 17 seconds relative to the untreated leg occurred in the circulation times to the feet of a series of patients on whom unilateral lumbar sympathectomies had been performed because of peripheral vascular disease.

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UNIPOLAR ELECTROCARDIOGRAPHY IN PULMONARY STENOSIS

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Congenital pulmonary stenosis with intact ventricular septum is a relatively common malformation of the heart. The stenosis varies from almost complete obliteration to a minimal decrease in the diameter of the orifice. The stenosis is usually of the valve, but it may be either of the infundibulum or of the lower bulbar orifice. The atrial septum may be complete, imperfectly developed, or it may be fenestrated: there is often anatomical patency of the foramen ovale, which may or may not allow the passage of blood from the right to the left atrium during life. The pulmonary artery beyond the stenosis is usually dilated and thin-walled, but it may be normal.

These variations make for wide diversity in the clinical features of the malformation. It is often a relatively benign lesion, but in its most severe form death occurs within the first year of life (Freed and Budnitz, 1946). Intermediate between these extremes is the group in which infancy is survived and childhood relatively symptomless but, sooner or later, there is increasing exertional dyspnœa, with or without cyanosis, leading on to congestive heart failure or sudden death. The work of Brock (1948, 1949) on valvulotomy and infundibular (or lower bulbar) resection has made this latter group of great clinical and diagnostic importance.

In spite of the anatomical and clinical variations, the increased work of the right ventricle depends essentially on the severity of the stenosis in relation to the right ventricular output. The extent of the right ventricular hypertrophy is, therefore, an indication of the severity of the lesion, even in the absence of disability, cyanosis, and clinical deterioration. By recording the degree and development of this hypertrophy, unipolar electrocardiography is of great assistance in the assessment of the malformation.

The purpose of this paper is to demonstrate the characteristic cardiographic pattern of the extreme right ventricular hypertrophy that develops in pulmonary stenosis. The significance of this pattern is discussed in relation to diagnosis, prognosis, and surgical treatment of this congenital defect.

Electrocardiographic Features

Dow *et al.* (1950) have demonstrated by cardiac catheterization that pulmonary stenosis may exist for many years without disability and without electrocardiographic evidence of right ventricular hypertrophy. There may be right bundle branch block (Blackford and Parker, 1941; Auerbach and Harper, 1947), or the cardiographic picture of moderate to marked right ventricular hypertrophy (Currens, Kinney, and White, 1945; Lowance *et al.*, 1948). Right ventricular preponderance with large, pointed P waves in lead II, a tendency to lengthening of the P–R interval, and frequent inversion of the T waves in leads II and III, have been described by Allanby and Campbell (1949); they also report tall R waves extending across the chest in the three cases in whom they recorded unipolar chest leads. In the most severe grades of pulmonary stenosis and atresia, comparable

* Work done during tenure of the Kirk Duncanson Research Fellowship of the Royal College of Physicians, Edinburgh.

standard lead patterns have been recorded in infancy (Freed and Budnitz, 1946; Brown, 1949). Selzer *et al.* (1949), using CR leads, recorded the pattern of extreme right ventricular hypertrophy.

It is considered that this pattern is characteristic in the fully developed picture of pulmonary stenosis with intact ventricular septum. The form of the limb leads may vary with the position of the heart, but the usual features are gross right axis deviation, tall, pointed P waves in lead II, S–T depression, and deep T wave inversion in lead III and usually in lead II. In the unipolar limb leads, aVR shows a variable Q, tall R, and upright or inverted T wave; aVL shows a small r, deep S, and upright T wave; and aVF shows a small q, tall R, S–T depression, and deep T wave inversion. The unipolar chest leads show the most marked changes of right ventricular hypertrophy seen in clinical cardiography. There are tall R waves, S–T depression, and deeply inverted T waves that extend far across the chest towards the left. The greatest degree of right ventricular hypertrophy is characteristically recorded from the left of the sternum—V2, V3, or even V4. Necropsy findings prove that the unipolar chest leads are thus faithful recorders of the hypertrophy of the underlying myocardium.

Case Summaries

Case 1. A boy, aged 5 years, who had experienced little disability apart from a tendency to fainting attacks on exertion. He was not cyanosed. There was gross cardiac enlargement and, on radioscopy, immense dilatation of the pulmonary artery. The electrocardiogram in Fig. 1* was recorded shortly before he dropped dead on his way to school.

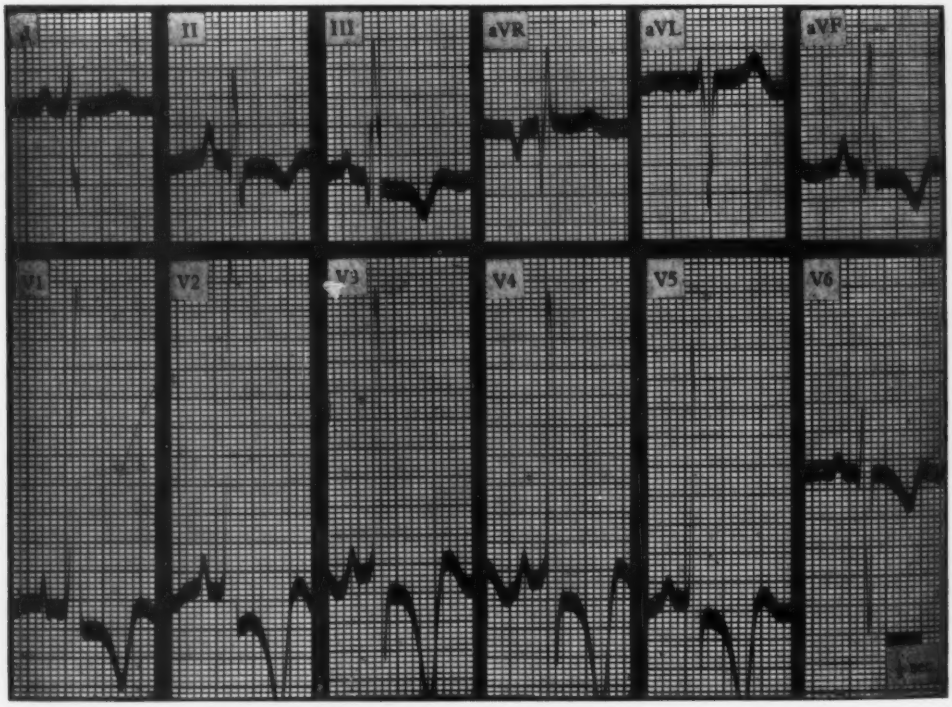


Fig. 1.—Electrocardiogram of Case 1. The fully developed pattern of extreme right ventricular hypertrophy. At necropsy there was valvular pulmonary stenosis, intact ventricular septum, closed foramen ovale, and post-stenotic dilatation of pulmonary artery.

* This electrocardiogram has been previously reported in a review of unipolar electrocardiograms (Hill, I. G. W. (1950), *Lancet*, **1**, 1027).

Post mortem, there was a severe grade of valvular pulmonary stenosis (diameter at apex of cone measured 3·5 mm.). The foramen ovale was anatomically closed and the right ventricular wall was approximately twice as thick as the left (average thickness, 16 mm.).

Case 2. A boy, aged 13 years, who had been cyanosed at rest and breathless on exertion since 6 months of age. These features became more striking when he started to walk at 12 months. Throughout his life he was severely handicapped, thin, and grossly underweight. He squatted in the best Fallot tradition. There was slight cardiac enlargement on radioscopy and the left pulmonary artery was dilated. His general condition deteriorated rapidly during the last year of his life. The electrocardiogram in Fig. 2 was recorded a few days before he died suddenly during thoracotomy.

Post mortem, there was a severe grade of valvular pulmonary stenosis (diameter at apex of cone

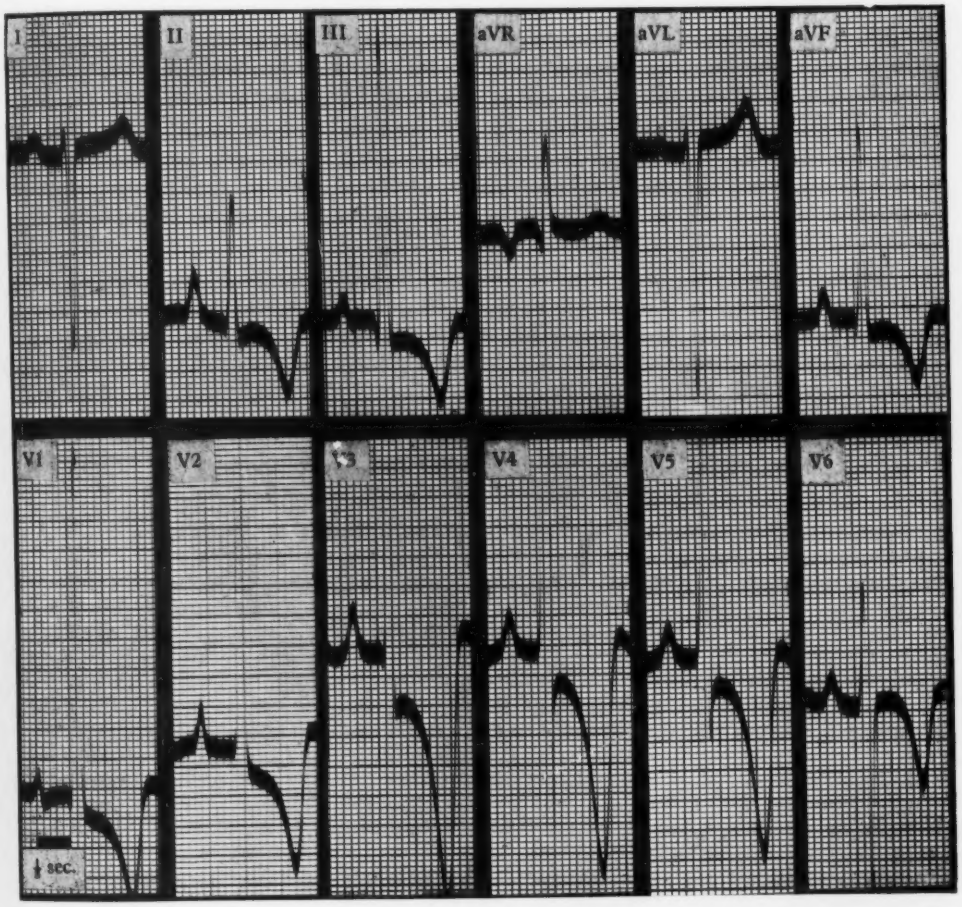


FIG. 2.—Electrocardiogram of Case 2. The fully developed pattern of extreme right ventricular hypertrophy. Voltage of QRS complexes in chest leads at normal sensitivity was such that the peaks of the R and S waves were not recorded. At 1/2 N sensitivity tall R waves extended from V1 to V5 as the main initial deflections. At necropsy there was valvular pulmonary stenosis, intact ventricular septum, fenestrated atrial septal defect, and post-stenotic dilatation mainly of left pulmonary artery.

was 3·5 mm.). There was a fenestrated atrial septal defect of 15 mm. diameter and the right ventricle was approximately twice as thick as the left (average thickness, 17 mm.).

Case 3. A boy, aged 5 years, in whom congenital heart disease was diagnosed for the first time on routine school medical examination. Since that time he had been thought to be slightly breathless and cyanosed on severe exertion. In spite of this he was a keen footballer and was able to play centre-half in his local school team. There was moderate cardiac enlargement, prominence of the conus of the right ventricle, but no dilatation of the pulmonary artery on radioscopy. During the next 6 years there was no change in his clinical or radiological features. The electrocardiogram in Fig. 3B was recorded when he was 12 years of age. A year later he died suddenly after attending a fair.

Post mortem, he had a severe grade of infundibular stenosis which involved the pulmonary

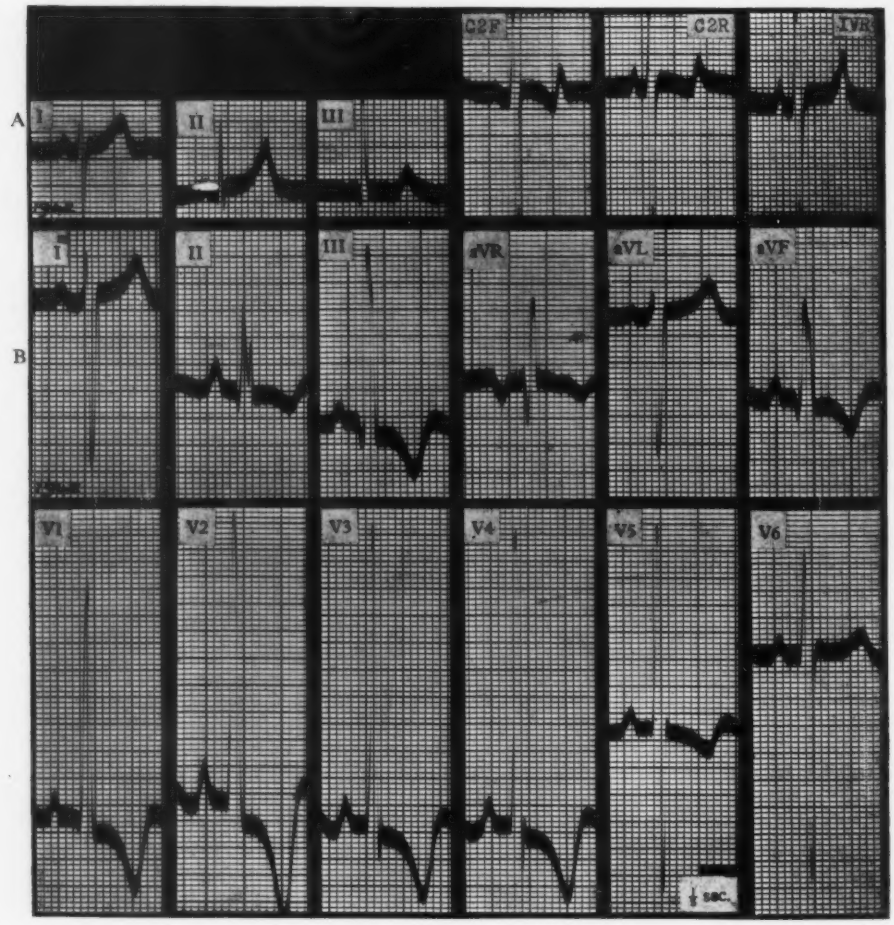
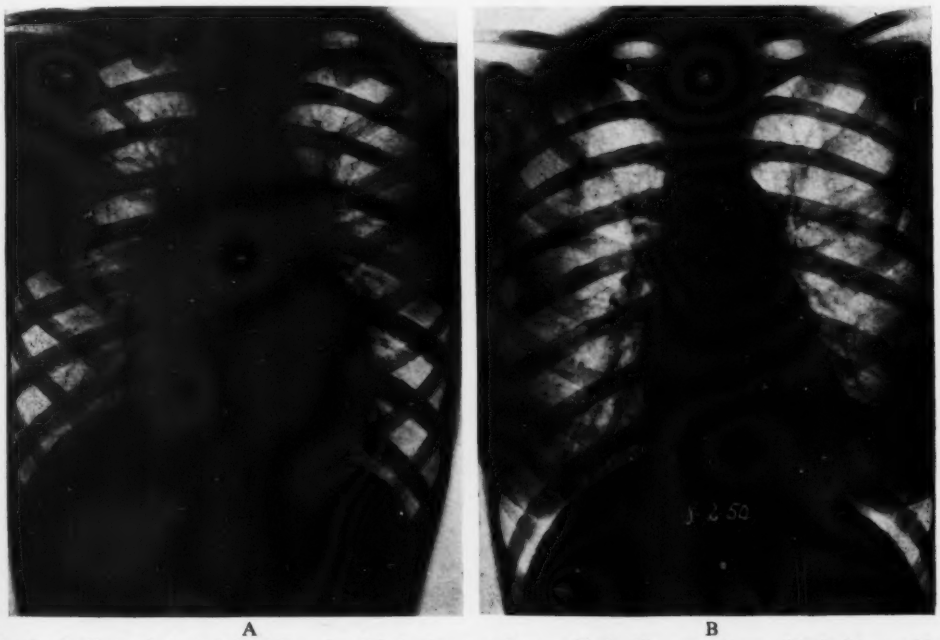


FIG. 3.—Electrocardiogram of Case 3. (A) At 5 years of age. Right axis deviation. Small P waves in lead II. (B) At 12 years of age. Extreme right ventricular hypertrophy. At necropsy there was infundibular pulmonary stenosis, intact ventricular septum, small valvular foramen ovale, without any post-stenotic dilatation of pulmonary artery.

valves, extended for 25 mm. into the right ventricle, and had a diameter of 5 mm. An anatomically patent foramen ovale measured only 2 mm. diameter and was covered by a well-formed septum secundum. The right ventricle was approximately twice as thick as the left (average thickness, 19 mm.).

Case 4. A girl, aged 9 years, when first seen in 1944. She was little disabled, except by an over-solicitous mother, and there has been no clinical deterioration during 6 years of follow-up. Radioscopic examination showed no increase in heart size (Fig. 4), but there have been well-marked



A B

FIG. 4.—Radiograph (anterior) of Case 4. (A) At 9 years of age. (B) At 15 years of age. Vertical type of heart shadow, prominence of right border, prominent pulmonary artery segment, diminished vascularity of lung fields. No increase in cardiothoracic ratio during 6 years of follow-up.

electrocardiographic changes. At 9 years of age (Fig. 5A), P wave was already more than 3 mm. in height in lead II and the T waves were inverted in leads III and C2F. Four years later, after a period of enforced, but unnecessary, invalidism, there had been no significant change in the standard leads; unipolar leads, which were then recorded for the first time, showed tall R waves followed by deep T inversion in V1 and V2, but not beyond. During the next two years her mother was encouraged to let her lead a more normal life and by 15 years of age the T wave had become inverted in lead II and tall R waves and inverted T waves extended across the chest to V5 (Fig. 5B).

Case 5. A girl, aged 9 years when first seen. At that time she experienced slight exertional dyspnœa but no real disability in spite of considerable cardiac enlargement (Fig. 6). Two years later her clinical and radiological condition remained unchanged but she was sometimes very tired after a full-length gymnastic class at school. Unipolar electrocardiograms, in contrast, revealed marked and rapidly developing changes (Fig. 7).

Case 6. A young married woman, aged 27 years when first seen. At that time she had given birth to two children with relative ease and was admitted to hospital on account of pulmonary tuberculosis. Electrocardiogram showed advanced changes of right ventricular hypertrophy with

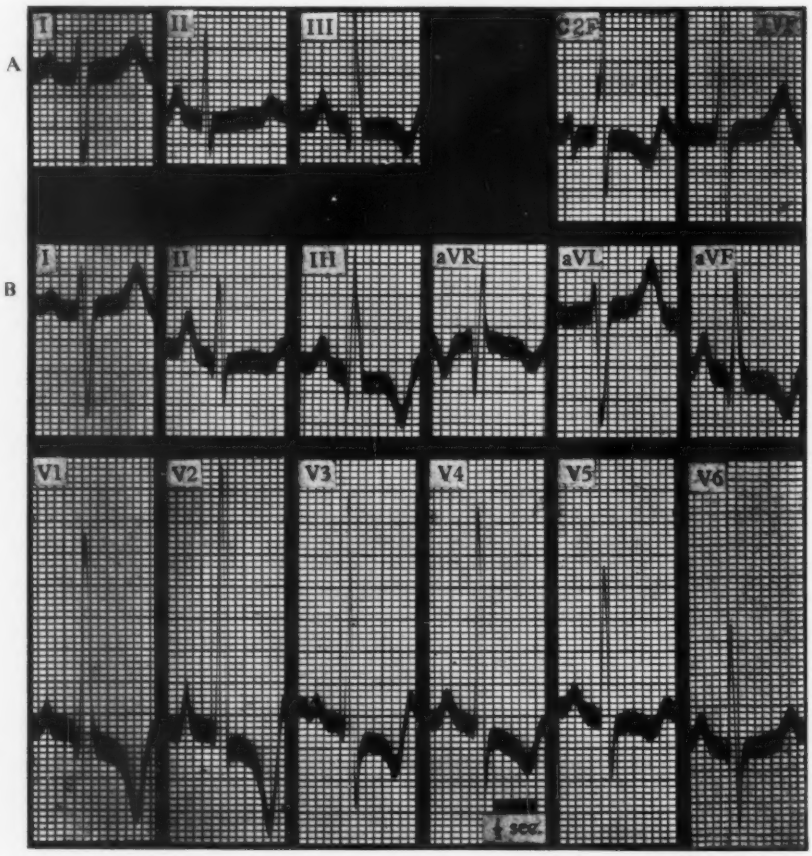


FIG. 5.—Electrocardiogram of Case 4. (A) At 9 years of age. Right axis deviation, P wave over 3 mm. in lead II, and inverted T wave in leads III and C2F. (B) At 15 years of age. Pattern of extreme right ventricular hypertrophy although the heart is not enlarged on radioscopy (Fig. 4).

P waves over 4 mm. in height in lead II, marked right axis deviation, S–T depression and inverted T waves in leads II, III, and C2F, and a sharply diphasic T wave in IVF. Radioscopy showed the size of the cardiovascular shadow to be within normal limits but the shape suggested right ventricular hypertrophy and the pulmonary artery was enlarged. During the next three years the pulmonary tuberculosis extended to involve both lungs. She had repeated hæmoptyses, increasing exertional dyspnœa, tiredness, and intermittent œdema of the ankles. She was never observed to be cyanosed. Her eventual death at 30 years of age was due to massive hæmoptysis.

Post mortem, there was valvular pulmonary stenosis of moderate severity (diameter at apex of cone, 8 mm.); anatomical patency of the foramen ovale which, although valvular in type, had a diameter of 9 mm.; the right ventricular wall was one and a half times as thick as the left (average thickness, 22 mm.).

Case 7. A boy, aged 13 years when he was first seen. At that time he had suffered from progressive exertional dyspnœa and cyanosis since 5 years of age. He was severely limited in his activities and complaining of frequent " dizzy turns " on exertion. Radioscopy showed slight

FIG. 6.—Radiograph (anterior) of Case 5 at 9 years of age. Considerable cardiac enlargement, increased convexity of right border of heart, well marked enlargement of pulmonary artery segment, and hilar shadows normal but small in relation to heart size. There has been no increase in heart size during two years of follow-up.

cardiac enlargement and prominence of the pulmonary artery and its left main branch. Cardiographic examination (Fig. 8A) showed well-advanced right ventricular hypertrophy with deep inversion of the T wave in C2F. Six months later he developed subacute bacterial endocarditis, but after a 28-day course of penicillin (0·5 mega units daily) made a remarkable recovery. Like the case reported by Pollack *et al.* (1948), the bacterial infection performed an effective " valvulotomy." Before the acute illness he could not run the length of a football field; after recovery he played a full game every Saturday. The T wave became less inverted in lead C2F. At 18 years of age he now admits to little cardiac disability, he is no longer cyanosed, and in spite of full-time work and greatly increased activity there has been no evidence of increased right ventricular hypertrophy (Fig. 8B).

DISCUSSION

These cases illustrate the developing and fully developed electrocardiographic pattern of extreme right ventricular hypertrophy common in the severer grades of pulmonary stenosis when the ventricular septum is intact. Their similarity suggests that the development of this pattern is independent of clinical or radiological variation, the state of the atrial septum, the exact site of the stenosis and, as would be expected, the state of the pulmonary artery beyond the stenosis.

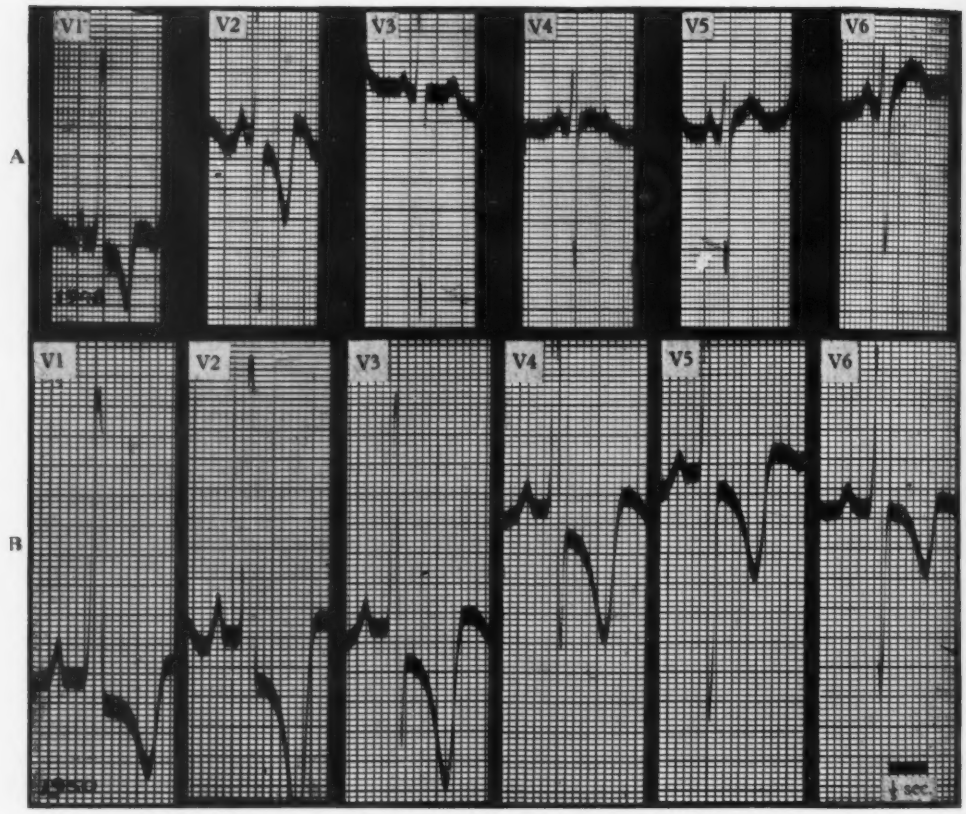


FIG. 7.—Electrocardiogram of Case 5. (A) At 9 years of age. (B) At 11 years of age. Follow-up during 2 years reveals rapid development of the full pattern of extreme right ventricular hypertrophy. Limb leads revealed no change in the position of the heart.

Variation in the position of the heart may alter the pattern of the standard and unipolar limb leads, as in Allanby and Campbell's (1949) Case 1, but the chest leads remain characteristic.

The size and shape of the hearts in the four cases with necropsy bore a close resemblance to each other and to those examples of this malformation reported elsewhere. The right atrium was enlarged and hypertrophied, there was enormous hypertrophy of the right ventricle and of the ventricular septum, which curved to the left as it approached the apex. This hypertrophied right ventricle thus formed the entire anterior surface and a large part of the diaphragmatic surface of the heart. The left side of the heart was within normal limits.

The time of onset of the intrinsic deflection in unipolar chest lead V1 was between 0·04 and 0·06 sec. in each case. In only two cases was there notching of the R wave in this lead (Fig. 7 and 8B) and even in these R′ never occurred later than 0·06 sec. The unipolar chest leads thus differed from the pattern of partial right bundle branch block common in large atrial and ventricular septal defects. It was considered that the extreme thickness of the right ventricular wall and the enormous size of the muscle cells could adequately account for the delay of the intrinsic deflection. In none of the specimens were serial sections of the conduction tissue examined.

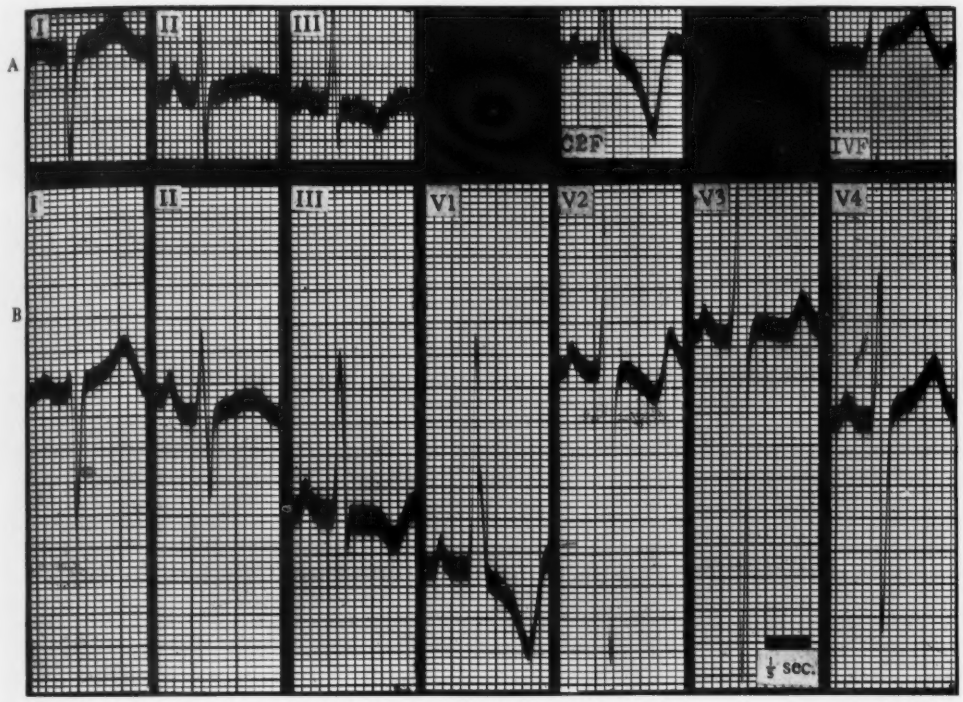


FIG. 8.—Electrocardiogram of Case 7. (A) At 13 years of age. Six months before onset of bacterial endocarditis. Right axis deviation and deep T inversion in C2F. (B) At 16 years of age. Right ventricular hypertrophy but not of extreme degree. Follow-up record at 18 years of age showed no change.

DEVELOPMENT OF ELECTROCARDIOGRAPHIC PATTERN

In the fœtal circulation, if we transfer the findings in lambs to the human subject, the right ventricular output is considerably less in the fœtus than in the new-born child. Franklin, Barclay, and Prichard (1946) have shown how the blood returning to the heart in the lamb fœtus is shared between the two ventricles; how the blood returning from the placenta and lower half of the body is divided by the caudal edge of the inter-atrial septum into a large stream that passes to the left side of the heart, and a small stream that is joined by the blood from the upper part of the body and passes into the right ventricle. With the opening of the pulmonary circulation at birth and the functional closure of the foramen ovale, the output of the right ventricle is immediately increased. Subsequent growth and activity of the child lead to further increase of the right ventricular output in relation to the relatively static or possibly decreasing (Allanby and Campbell, 1949) size of the stenosed pulmonary orifice. It is suggested that the pulmonary opening may be significantly narrowed in intra-uterine life without stimulating hypertrophy of the right ventricle; that the right ventricle after birth is able to overcome mild degrees of stenosis without developing sufficient hypertrophy for electrocardiographic detection; but that in the more severe grades of stenosis there is a progressive hypertrophy of the right ventricle.

Unipolar electrocardiography, by revealing the degree of this hypertrophy is of very great value in the assessment of the severity of the stenosis. In mild cases the pattern of extreme right ventricular hypertrophy never develops; in moderately severe cases it develops slowly and does not

reach its peak until adult life; in severe cases it develops rapidly and in childhood; in extreme cases it is present from birth or develops within the first few months of life.

This is not the invariable course. In pulmonary atresia and rare cases of pulmonary stenosis, a greatly increased amount of blood may pass through the foramen ovale to the left side of the heart. There is deep cyanosis from birth, the right ventricle becomes atrophic and the left ventricle hypertrophies. Peacock (1866) gave a good example and quoted several others. Survival beyond the first few days of life is rare and the case reported by Wood (1942), which survived to 6 years of age, is very unusual. More commonly the right atrium persists in feeding the right ventricle.

Unlike lesions that lead to pulmonary congestion, dyspnœa is a relatively late symptom in pulmonary stenosis, and patients with this malformation may lead comparatively normal lives until the right ventricle begins to fail. In the absence of tricuspid incompetence or rheumatic or bacterial endocarditis, congestive heart failure does not occur until the right ventricle has reached its maximum degree of hypertrophy. By revealing the development of this hypertrophy, unipolar electrocardiography provides evidence that precedes change in either the clinical or radiological condition of the patient (Cases 4 and 5). Once the full hypertrophy has developed it may be sufficient to overcome the stenosis for many years (Case 6); especially if the hypertrophy develops slowly and does not reach the extreme degree until adult life. If, on the other hand, the hypertrophy develops rapidly and in childhood, there is the danger of early congestive failure. Cases 1

A B

FIG. 9.—Photomicrographs of myocardium (×90) of right ventricle and stained with Weigert's iron hæmatoxylin. (A) Case 3. Large muscle cells but no diffuse fibrosis. (B) Case 6. Large muscle cells with extensive fibrosis.

and 3, Blackford and Parker's (1941) case, Allanby and Campbell's (1949) second case, and the frequency of abrupt cardiac arrest during thoracotomy, suggest that sudden death is more common in this malformation than has been recognized. Acute right ventricular failure appears the most likely explanation.

Allanby and Campbell (1949) have pointed out the frequency of prolongation of the P–R interval. This has not been a feature of the cases reported here, the longest intervals being 0·2 sec. in Case 2 and 0·18 sec. in Case 6. In the remainder it was 0·16 sec. or less.

A more significant difference between these cases and those reported by Allanby and Campbell (1949) is the relative absence of diffuse fibrosis through the myocardium of the right ventricle (Fig. 9). The only heart in which diffuse fibrosis was a striking feature was that from Case 6, the oldest patient, in whom there had been long-standing right ventricular failure. Taken with the cases in which diffuse fibrosis has been reported, this suggests that it is the result of long-standing over-work and not an inherent part of the hypertrophy of the right ventricular wall.

Differential Diagnosis

The right ventricle seldom reaches so marked a degree of hypertrophy in any other lesion, congenital or acquired, as it does in isolated pulmonary stenosis. The pattern of extreme right ventricular hypertrophy described, although characteristic of the severe forms, is not seen frequently in clinical cardiography, though it can occur in other lesions.

In the tetralogy of Fallot, the ventricular septal defect and over-riding aorta spare the right ventricle at the expense of the pulmonary circulation. The arterial anoxæmia, secondary polycythæmia, and diminished pulmonary blood flow, are usually responsible for death before the right ventricle fails. Post mortem, the right ventricular wall is seldom thicker than the left, with which it shares its work. The degree of pulmonary stenosis, the size of the ventricular septal defect, and the extent of dextro-position of the aorta, all affect the burden carried by the right ventricle in the tetralogy. This is seen electrocardiographically in a great diversity of patterns of right ventricular hypertrophy. Usually there are tall R waves and inverted T waves in V1 (Fig. 10) with an abrupt

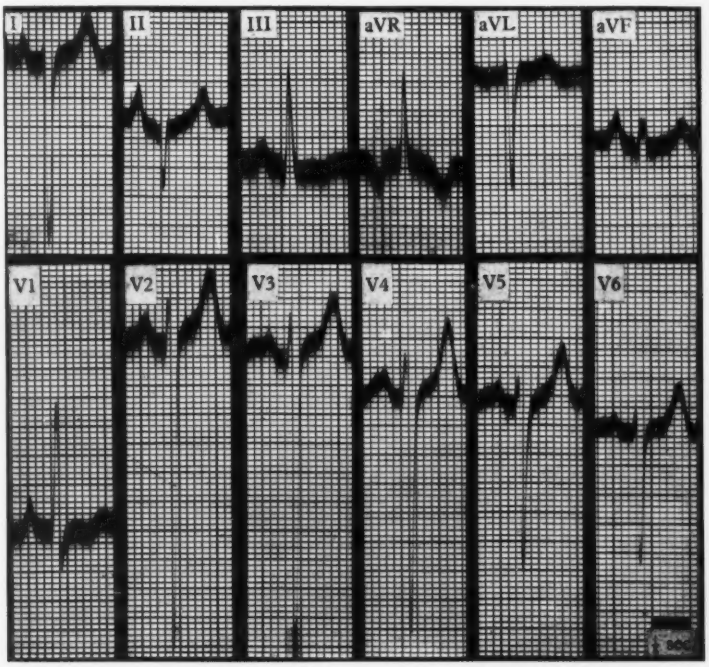


Fig. 10.—Electrocardiogram of girl, aged 12 years, with the tetralogy of Fallot (necropsy confirmation). Most of her life spent in wheel-chair. Frequent cyanotic attacks with loss of consciousness. Death after operation. Note the tall R wave in V1 with abrupt change to small r with deep S waves in V2. Tall R as sole initial deflection in aVR. Deep S in V6.

change to small r and deep S waves in V2 or V3. In certain cases the cardiographic diagnosis of right ventricular hypertrophy depends on the recognition of deep S waves in V6 and tall R waves in aVR. Kossmann *et al.* (1948) give a good example of the abrupt change between V1 and V2 and the characteristic tall R waves in leads V3R to V6R.

The author has not seen the pattern of extreme right ventricular hypertrophy in any case of the tetralogy that has come to necropsy. Nevertheless, clinical experience suggests that it does sometimes occur, possibly when the ventricular septal defect is small and the aorta relatively little

dextroposed, possibly when there is extreme dextroposition of the aorta and the right ventricle is responsible for both systemic and pulmonary circulations. Whatever the cause this pattern is rare in the tetralogy and common in isolated pulmonary stenosis; its recognition is of value in their differentiation.

In atrial septal defect the work of the right ventricle is added to by its greatly increased output and sometimes by a rise of peripheral resistance in the lungs. Burrett and White (1945) have suggested that pulmonary arterial sclerosis and vascular thrombosis are common. The author has not, however, seen this pattern of extreme right ventricular hypertrophy in atrial septal defect, though Goldberger (1947) has given an example.

In mitral stenosis electrocardiographic evidence of right ventricular hypertrophy is exceptional and slow to develop. Advanced changes do occasionally occur and the pattern of extreme right ventricular hypertrophy has been seen. In some such cases pericardial adhesions surrounding and constricting the pulmonary artery (Gouley, 1937) may be partially responsible.

In chronic cor pulmonale death is precipitated by the associated pulmonary disease before the right ventricle reaches the extreme degree of hypertrophy, but in idiopathic pulmonary hypertension electrocardiographic changes comparable to those recorded over the left ventricle in systemic hypertension may occur in the right chest leads.

Surgical Significance

Brock (1948, 1949) has shown that pulmonary valvulotomy and infundibular (or lower bulbar) resection are feasible operations. The operative mortality rate is reported as high and the risks involved are only justified in cases in which the outlook is poor.

Once the electrocardiographic pattern of extreme right ventricular hypertrophy has developed in pulmonary stenosis, the severity of the lesion is sure. It is suggested that surgery at this stage is justified in the younger age groups and that, by anticipating clinical deterioration and myocardial fibrosis, the operative mortality rate might be reduced.

From the point of view of surgical follow-up, Case 7 is of great interest. This boy's progress, which has been followed electrocardiographically, suggests, as would be anticipated, that in spite of increased activity and growth the progressive hypertrophy of the right ventricle can be arrested by enlargement of the pulmonary orifice.

Summary

The electrocardiographic features of seven cases of congenital pulmonary stenosis with intact ventricular septum are reported in illustration of the pattern of extreme right ventricular hypertrophy common in this malformation. The chief characteristics of this pattern are seen in the chest leads: they show tall R waves, S–T depression, and deep inversion of the T waves extending far across the left side of the chest.

The diagnosis is supported by necropsy findings in four of the cases.

It is suggested that the right ventricle hypertrophies in proportion to the degree of the stenosis in relation to the right ventricular output, and that unipolar electrocardiography, by recording the extent of the hypertrophy, affords an accurate measure of the severity of the stenosis.

Evidence is presented to show that the development of the electrocardiographic pattern described precedes clinical deterioration, change in the radiological appearance of the heart, onset of right ventricular failure, and diffuse fibrosis of the myocardium. This pattern is characteristic irrespective of heart size on radioscopy, patency of the foramen ovale, exact site of the stenosis, and the state of the pulmonary artery beyond the stenosis.

The significance of this electrocardiographic pattern is discussed in relation to diagnosis, prognosis, and surgical treatment of the malformation.

In the absence of necropsy material, the electrocardiographic pattern of fully developed right bundle branch block, which sometimes occurs in this malformation, is not considered in this paper.

I wish to express my thanks to Dr. A. Rae Gilchrist for his help and encouragement in the preparation of this paper and for permission to report Cases 2, 3, 4, 5, and 7; to Dr. I. G. W. Hill for helpful criticisms on the electrocardiograms and for permission to report Case 1; to Dr. John Duckworth for anatomical examination of the specimens and the preparation of Fig. 10; to Dr. Fergus Hewat for access to his clinical records of Case 6; to Mr. Andrew Logan for permission to examine the heart in Case 6; to Mr. R. P. Danskin and the staff of the Electrocardiograph Department of the Royal Infirmary, Edinburgh, for their infinite pains in the preparation of the electrocardiograms.

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CASE REPORTS

COMPLETE A-V DISSOCIATION IN ACUTE RHEUMATISM

BY

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In acute rheumatism, dissociation can occur between the action of the auricles and ventricles as a temporary or permanent effect. The dissociation may be complete or partial, and the resulting rhythm will depend on the relative rates of the S-A and A-V nodes and on the presence and degree of conduction disturbance between these two nodes.

In complete auriculo-ventricular dissociation (usually termed complete heart block), the auricles and ventricles are totally independent. The auricles respond to the sinus stimulus and with it may show respiratory arrhythmia, while the A-V node is in control of the ventricles and discharges itself more regularly. The ventricular rate is classically slower than the auricular and it is usually very slow. This very slow pulse, however, is less constant in rheumatic cases, and Crawford and Di Gregorio (1947) describe ventricular rates within the normal range, one woman of 29 having a pulse rate of 81. In the present case, the ventricular rate exceeded that of the auricles.

Case Report

Geoffrey S., aged 9, was admitted on 7/4/49. There was no past or family history of rheumatism, but he had had recurrent sore throats and lived in a damp squatter's hut. For some months he had been vaguely unwell, with pallor, lassitude and nervousness. On 5/4/49 he again developed a sore throat with fever, headache, vomiting, and pain in the legs. On the day of admission both feet and the left knee had become swollen so that he could not walk.

On examination he was ill, pale, and sweating, with a temperature of 102°F. His pulse was regular and compressible, its rate being 120 a minute. The heart was slightly enlarged, and there was a soft apical systolic murmur and a loud split pulmonary second sound. The blood pressure was 110/60. The tonsils were infected. The right ankle was hot and swollen but not very painful. A blood count was normal, but the erythrocyte sedimentation rate was 39 mm. in one hour. He was regarded as a case of rheumatic fever and treated with calcium aspirin.

The electrocardiogram on the day of admission (Fig. 1) showed complete auriculo-ventricular dissociation, with a ventricular rate of 112 and an auricular rate of 103. The auricles showed slight respiratory arrhythmia, but the ventricles were regular. No clinical note was made of variability of the heart sounds, and this peculiar rhythm had not been suspected.

On 8/4/49, the left knee was involved. By 11/4/49, the temperature was subsiding, but he was drowsy and confused: salicylates were therefore stopped. The cardiogram now showed a sinus rhythm with a P–R interval of 0·28 second.

By 14/4/49, the pulse was much slower, with prominent respiratory arrhythmia, and the P–R interval had shortened to 0·25 sec. (Fig. 2). Bradycardia persisted, but the P–R interval shortened steadily to 0·20 sec. on 22/4/49, and 0·18 sec. on 13/5/49. By this time his heart rate had risen from

FIG. 1.—Cardiogram on day of admission, showing complete A-V dissociation. Auricular rate: 103; ventricular rate, 112.

50 to 80, and the E.S.R. had become normal. He was allowed up gradually and transferred for convalescence on 7/6/49.

When last seen (20/7/49) he was very well, with a heart of normal size, a barely audible systolic murmur at the apex, and an E.S.R. of 3 mm. in one hour.

Discussion

In certain cases of rheumatic fever, the periodicity of the A-V node is increased above that of the S-A node, and in these the heart's action and the electrocardiogram depend on the presence and degree of auriculo-ventricular block. If there is no block, the whole heart is governed by the A-V node and the result is nodal rhythm.

If there is only retrograde block between ventricle and auricle, then the faster ventricular beats will not interfere with the slower auricular contractions. However, at intervals the impulse from the S-A node will reach the A-V node before it has discharged itself, but after its refractory period: the ventricle will then respond with a premature contraction and then resume its A-V nodal rhythm without a compensatory pause. This arrhythmia is usually called interference dissociation. Unfortunately the nomenclature is confused. Interference dissociation may be called "complete A-V dissociation" (Zuidema, 1949) although the dissociation is not complete. Kirby (1948) calls it "ventricular escape." Thus one may be uncertain of the exact arrhythmia under discussion unless electrocardiograms are reproduced. Since the term interference dissociation implies the two main features of the abnormal rhythm, it would seem the most reasonable name to use.

Transient ventricular escape is more common and may occur in normal subjects, as for example when deep expiration causes such vagal inhibition of the S-A node that it is temporarily producing stimuli more slowly than the A-V node. In interference dissociation, the A-V node is the more irritable of the two for a longer period—perhaps several days (Cutts, 1937).

Interference dissociation has been reported in 6–12 per cent of various series of cases of rheumatic fever, almost always as an early finding (Oettinger and Neslin, 1932; Wendkos and Noll, 1944; Stein and Bartlett, 1946). Cutts (1937) reports 12 cases of this and similar rhythms, 6 arising during

rheumatic fever: moreover, all these six were febrile. He goes so far as to say that interference dissociation in a young person is highly suggestive of rheumatic fever. The latest report is that of Kirby (1948), whose Case 1 presented typical interference dissociation, and is one of the few described where this anomaly of rhythm has been found in a child. His Case 2 seemed rather different —an arrhythmia arose terminally in a fatal attack of rheumatic fever, the ventricular rate being slower than the auricular, and an occasional beat being dropped as in a Wenckebach period. This periodicity was later evident clinically when every sixth beat was dropped, but unfortunately no electrocardiogram was published corresponding to this clinical finding.

FIG. 2.—Cardiogram one week after admission, showing sinus rhythm at a rate of 80. Prolonged P–R interval of 0·25 sec.

It is reasonable to suppose that the rheumatic process is responsible for both depressing conduction and irritating the A-V node till its periodicity is faster than that of the S-A node. The former effect is still evident after reversion to sinus rhythm in the finding of a prolonged P–R interval. How the effect on the A-V node is produced is unknown. Certainly the lesions in the bundle of His described by Gross and Fried could not cause A-V dissociation, nor does their occurrence in necropsy material prove their existence in the early stages of rheumatic polyarthritis.

In our case, the disease seems to have caused increased periodicity of the A-V node, and also total auriculo-ventricular block, so producing complete heart block with ventricular rate greater than that of the auricles. This arrhythmia (if a regular rhythm can be called such) was undiagnosed clinically. Its finding seemed to confirm the diagnosis of rheumatic fever which had been questioned because of the relative painlessness of the joints.

As has been found in the rheumatic cases of interference dissociation, this anomaly of rhythm was transient and occurred early in the disease when fever was present. It was followed by evidence of conduction disturbance in the long P–R interval, but this disappeared and the heart seems to have been left with minimal damage. It would seem that both interference dissociation and the type of rhythm shown by this case may not have an unfavourable significance. Since both seem to occur early in the illness, perhaps often before the patient is transferred to hospital, they may well be more common than published reports would indicate.

Summary

A case is reported of transient total A-V dissociation, occurring on the first day of acute rheumatic fever in a boy of 9 years, in which the ventricular rate was faster than the auricular.

No previous record of an exactly similar case has been found.

The mechanism of origin of this disturbance of rhythm and of interference dissociation is discussed.

I wish to thank Dr. W. G. Wyllie for permission to publish this case.

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ACUTE BACTERIAL ENDARTERITIS

BY

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Abnormality of a valve predisposes to bacterial endocarditis, even when mechanical beating action is absent, as in destruction of a cusp by previous rheumatic disease. Yet the formation of vegetations at sites other than valvular endocardium is rare ; and, in spite of the frequency and apparent suitability of aortic ulcers, no report of bacterial endarteritis upon simple atheroma has been found in the list of aortic diseases in the *Index Medicus* covering the last ten years. However, Sherf and Boyd (1948) say that, in rare cases, acute bacterial endarteritis develops on the basis of syphilitic aortitis or of atheroma. White (1945) points out that the aortic intima may be involved in the endocarditis and that ulceration of the valve, the heart wall, or the wall of the aorta is common in more severe cases. He does not mention an acute endarteritis as occurring in the absence of an endocarditis. Neither do Libman and Friedberg (1941) mention this possibility.

Case Report

The present case was discovered unexpectedly at necropsy. A male, aged 51, with a twenty-year history of abdominal pain, was admitted to hospital for partial gastrectomy. The operation was performed after transfusion of three pints of blood. A chronic duodenal ulcer, perforating the head of the pancreas, was found. Following operation, fever and cough developed ; X-ray of the chest showed no evidence of lung disease, two days later. The fever settled and the patient departed for convalescence on the thirteenth day.

After a further nine days, he was re-admitted with pyrexia. One week after re-admission the leucocytes had risen to 26,000, X-ray of the chest was still negative, and a subphrenic abscess was suspected.

Fourteen days after re-admission fluid developed at the right lung base and obscured the movements of the diaphragm. The fluid contained many polymorphonuclear cells ; culture was sterile. Penicillin therapy was started. Next day surgical explorations of the subphrenic region and of the abdominal cavity were carried out ; no abnormality was detected. After these operations there was peripheral circulatory collapse. Transfusion of four pints of blood was given but the patient died two days after the second and forty-one days after the first operation. Throughout the illness there was no clinical evidence of embolism.

Post-mortem Findings

Necropsy was performed the day after death. There was an adherent pericardium, the two layers of which were completely fused by tough, fibrous adhesions separated from the muscle by a layer of fat 2·5 cm. thick. Coronary atheroma was slight to moderate. The right pleural sac contained about one pint of thin pus, the right lung being covered by fibrinous adhesions with some gelatinous pockets defined by old fibrous adhesions. A lung abscess, 5 cm. diameter, was situated about the middle of the posterior half of the right lower lobe and bounded behind by thin pleura

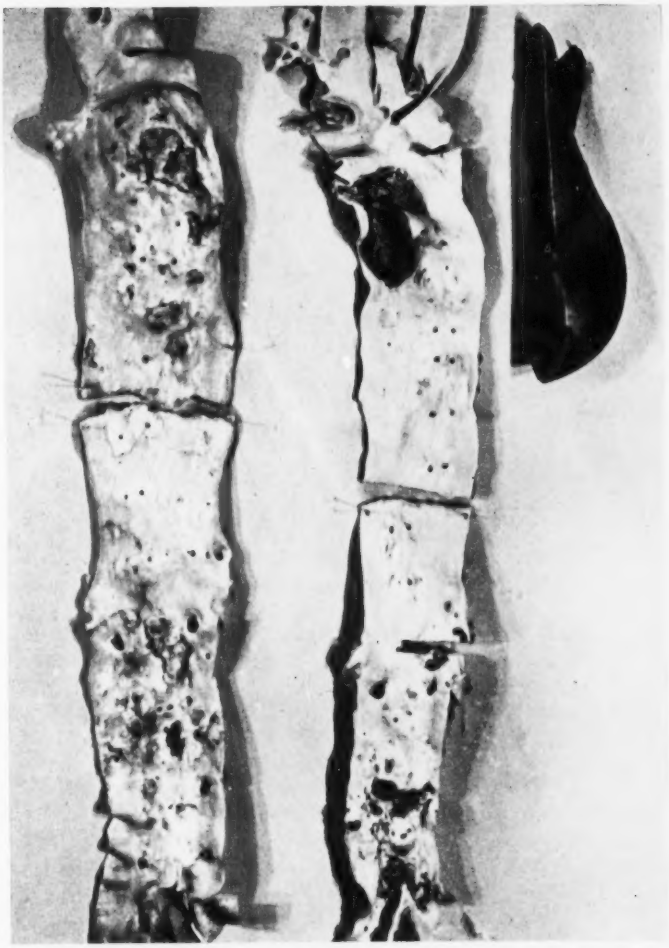

FIG. 1.—(Centre) Aorta of this case. (Left) Aorta from another body showing severe degree of pure atheroma (for comparison). (Right) One of the liver infarcts.

only. The remainder of the wall was composed of firm granulation tissue up to 0·5 cm. thick, and the cavity contained grey fluid pus.

Two large and striking vegetations, resembling those of subacute bacterial endocarditis, were found springing from the aortic intima at a point opposite the origin of the left subclavian artery (Fig. 1). Both were roughly spindle-shaped polyps of blood clot, 3·5 cm. long by up to 2 cm. diameter, lying free in the aortic lumen, except for the attachment of their upper ends to the same atheromatous patch, about 1 cm. diameter, in the aortic wall. Their appearance was that of sausage-meat, fleshy and pink, with some reticulation and a few adherent wisps of black post-mortem clot ; their consistency was that of a typical friable thrombus, and their surfaces were slightly facetted by being pressed together and against the neighbouring wall. The thoracic aorta showed calcifying atheroma with little ulceration. In the abdominal aorta atheromatous ulcers

were numerous and several of them were covered by the warty thrombi which commonly build in this situation, while others bore the friable clot of early vegetations similar to the large pair already described.

Numerous pale infarcts, 3 cm. in diameter on the average, with hæmorrhagic borders, were found in the liver (shown in Fig. 1.), and similar smaller infarcts in the cortex of both kidneys. There was infarction of the terminal 100 cm. of the ileum.

Microscopic sections showed a few nests of up to 50 gram-positive cocci in the lining of the lung abscess, the wall of which consisted of chronic pyogenic granulation tissue. The earlier sections through the attachment of one of the polypoid thrombi to the aortic wall failed to reveal any organisms. Many sections were cut and stained before it was found possible to demonstrate organisms. This was finally done by use of Weigert-Gram stain without counter-stain, when they were found in fairly numerous but very small clumps of less than one dozen gram-positive cocci at a time, sometimes in single pairs, round the border (but not in the substance) of the vegetation and also on the free border of the adjoining ulcerated aorta. The opinion reached was that these cocci were streptococci, since the majority were small and tended to be in short chains, although there were a very few clumps of larger more staphylococcal appearance. In one place three bacillary end-to-end forms were noted, such as are seen especially with *S. viridans*. The vegetation itself differed from control sections of the common plateau-clot seen on aortic ulcers in only one other particular, namely, that the fibrin had a pronounced reticular pattern throughout, corresponding to the " fish-scale " macroscopical appearance of the thrombus. In case and controls alike, the whole thrombus was freely peppered by polymorphs.

Sections of the aortic wall at the attachment of the vegetation showed (*a*) the changes of atheroma in the calcifying stage, and (*b*) an infiltration of chronic inflammatory cells, mainly in connection with the vasa vasorum, and occurring chiefly in two regions ; the adventitia and the intimal-medial junction. The monocyte was the commonest of these cells, though there were also numbers of plasma cells, lymphocytes and fibroblasts. In a few places, small collections of polymorphs were seen, but always within the lumen of a vessel.

The diagnosis offered on the above findings is that of acute bacterial endarteritis of the thoracic aorta, secondary to lung abscess.

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HYDATID HEART DISEASE WITH PAROXYSMAL TACHYCARDIA

BY

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Hydatid disease involving the heart is rare, although several isolated cases have been recorded: that of Neisser (1877). The heart may be affected by development of a cyst in or close to the myocardium. We wish to report a case where paroxysmal tachycardia was associated with hydatid cyst involving the myocardium.

Case Report

The patient was a butcher, aged 22 years, who had been employed at the local *abattoir*. He was admitted to hospital complaining of palpitation, cough, and dyspnœa of three days' duration. During this time he had suffered from several attacks of vomiting and on the day of admission had noticed that his legs had become swollen. Within the previous twelve months he had experienced three similar but less severe attacks which had lasted only a few hours. He could recall no other illnesses.

Examination disclosed an axious, well-built man who, during attacks of coughing, was expectorating blood-stained sputum. He was cyanosed and orthopnœic; his respiratory rate was sixty a minute. His temperature was 37° C. and the pulse, which was of poor volume, was regular at 220 beats a minute. There was engorgement of the cervical veins and the enlarged liver was tender and pulsatile. The legs were œdematous but there was no ascites. The lung bases were found to be congested. The cardiac impulse was in the fifth space in the mid-clavicular line. A loud systolic murmur was heard over the whole front of the heart. Except for inflamed and prolapsed internal hæmorrhoids, there were no other abnormal physical findings.

The leucocyte count was 13,600 per c.mm., with 78 per cent polymorphs; no eosinophil cells were seen. On fluroscopy, the heart was found to be symmetrically enlarged, with uniform pulsation of the cardiac borders. There was congestion of the lung fields. The electrocardiogram was that of a regular tachycardia at the rate of 214 beats a minute, and the ventricular deflections were 0·12 seconds wide. In lead CR1 small deflections producing slight notching on the ascending limb of the QRS complex could be recognized. The graph was consistent with a supraventicular tachycardia with 1: 1 response. An alternative but less likely diagnosis was that of ventricular tachycardia.

Course and Treatment. A progressive deterioration in the patient's condition occurred in spite of the therapy given. In addition to general symptomatic treatment, the following measures and drugs were serially employed: (1) carotid sinus and ocular pressure both before and after 0·5 mg. prostigmine, (2) the intravenous administration of 0·25 g. acetyl choline, (3) a full digitalising intravenous dose of cedilanide, (4) oral quinidine, 0·3 g. 3 hourly for 48 hours, (5) potassium acetate 0·2 g. 2 hourly for 24 hours, and (6) magnesium sulphate, 4 c.c. of 50 per cent solution administered intramuscularly on two occasions.

These procedures having failed to modify the increasing congestive failure, it was decided to give 0·2 g. quinidine hourly. A total of 1·6 g. was administered and, in spite of the pulse slowing to 130 a minute, the patient's condition failed to improve. He died 17 days after the onset of the attack.

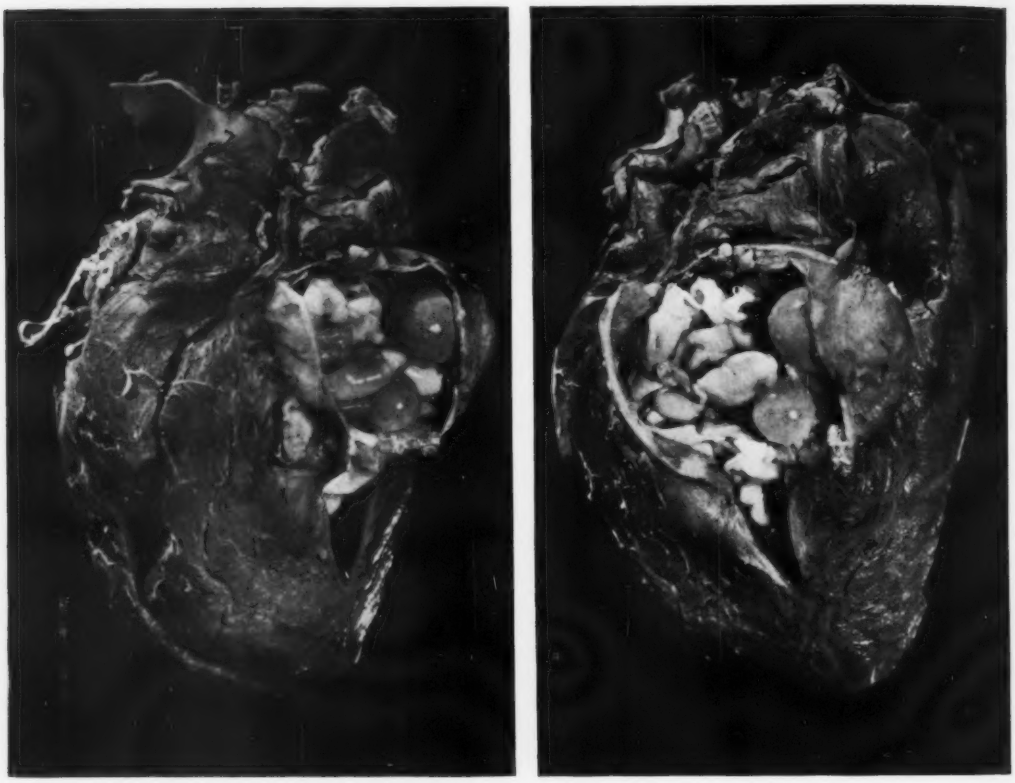

FIG. 1.—Two views of the heart from behind, after incision of the swelling, showing typical hydatid cysts with multiple daughter cysts.

Post-mortem Findings. At necropsy the viscera showed the congestive changes typical of heart failure. The heart was enlarged and protruding from its posterior surface was a cystic swelling about 5 cm. in diameter. An incision into the swelling, which had developed in the myocardium at the base of the left ventricle, showed it to be a typical hydatid cyst containing multiple daughter cysts. The cavities of the heart were free from ante-mortem thrombus. No hydatids were found in any other organ.

Comment

In hydatid disease the heart may be affected by development of a cyst in or close to the myocardium. The cardiac involvement has usually been symptomless, unsuspected, and not directly related to the cause of death (King, 1941). Alternatively, the rupture of a cyst in an organ remote from the heart may result in a sudden, fatal embolisation of daughter cysts into the blood stream. Such a mechanism has recently been reported (Khalil, 1941).

A correct ante-mortem diagnosis of hydatid cyst involving the heart has been made only once (Marten and de Crespigny, 1921). In this case the size and position of the cyst was such as to allow it to be recognized radiologically.

The present case is considered to be of interest in that it is the first in which paroxysmal tachycardia has been associated with a hydatid cyst involving the myocardium.

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INTERLOBAR HYDROTHORAX IN CARDIAC FAILURE

BY

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Interlobar hydrothorax in cardiac failure is not common: White, August, and Michie (1947) did not encounter it in a series of 100 cases of hydrothorax in cardiac failure. The following case report illustrates the condition and the problems that may arise in diagnosis.

A male, aged 68, was referred to the Royal Infirmary, Edinburgh on November 19, 1948. For some months he had felt vaguely unwell with loss of appetite, but without any complaint referable to the cardiovascular or respiratory systems. His past health had always been good, except for an attack of jaundice two years previously, diagnosed as infective hepatitis. Clinical examination was normal. A barium meal showed no abnormality, but during screening the radiologist observed an opacity in the chest. Because of this, a chest X-ray was taken and showed (Fig. 1) an effusion between the upper and middle lobes on the right side; the cardiac shadow was seen to be enlarged.

Despite the negative chest history, the possibility of an interlobar empyema was considered, but diagnostic aspiration revealed a clear fluid which was examined with the following results: sterile on culture; no clot on standing; protein 1·25 g. per 100 ml.; and cell content, 100 per cu. mm. with 70 per cent endothelial cells and 30 per cent small lymphocytes. The fluid was considered to be a transudate of unknown ætiology. No treatment was prescribed.

The patient reported on December 10, 1948. He now complained of dyspnœa on exertion. Clinical examination showed bilateral basal crepitations which had not been present previously; the cardiovascular system was again found to be normal (no clinical evidence of the cardiac enlargement known to be present could be found). An X-ray of chest (Fig. 2) showed a considerable increase in the interlobar effusion with small additional effusions in both costophrenic angles and general vascular congestion in the lungs.

A tentative diagnosis of early congestive cardiac failure was made. The patient was asked to rest in bed at home.

He reported on January 11, 1949. The dyspnœa was now more troublesome. Clinical examination revealed deterioration in his condition. The pulse was irregular; the neck veins were distended; the liver was palpable two inches below the costal margin; there was pitting œdema of the ankles and some ascites. There was now no doubt about the presence of congestive heart failure. The urine contained no sugar or albumin. An X-ray of chest showed no change from Fig. 2. An electrocardiogram showed slow auricular fibrillation with evidences of an old apical infarct. Estimation of plasma proteins gave albumin 3·9 and globulin 2·0 g. per 100 ml.

A diagnosis of congestive cardiac failure secondary to old myocardial infarction and fibrosis was made. Treatment in hospital with digitalis and mersalyl resulted in rapid improvement. An X-ray of chest three weeks later showed disappearance of the fluid in the costo-phrenic angles and lessening of the interlobar effusion. After the initial rapid improvement progress was slow, and some œdema of the ankles and enlargement of the liver persisted despite intensive therapy. These features were still present when he was discharged two months later. Administration of digitalis and mersalyl was continued at home.

He reported again in November, 1949. He was now symptom free and had no signs of cardiac failure although slow auricular fibrillation was still present. An X-ray of chest showed that the interlobar effusion had disappeared, leaving some thickening of the interlobar fissure; cardiac enlargement was still present.

FIG. 1.—Shows a moderate-sized interlobar hydrothorax and a little enlargement of the heart without much general pulmonary congestion, before general signs of congestive failure had developed, November 19, 1948.

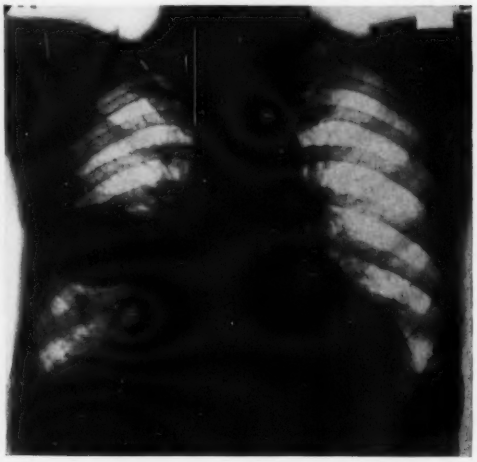

FIG. 2.—Shows an increase in size of the interlobar hydrothorax and of the pulmonary congestion when signs of congestive failure had become more evident, December 10, 1948.

Discussion

Including the case described above, 36 cases of cardiac interlobar hydrothorax have been reported—Helm (1917), Fleischner (1926), Stewart (1928), Kiser (1929), Freedman (1931), Steele (1932), Vesell (1932), Austrian (1932), Stein and Schwedel (1934), Shiflett (1935), Levitin (1937), Bedford and Lovibond (1941), Russakoff and Weinberg (1944). In 24 of the 29 cases in which the site was given, the interlobar fluid was in the right lesser fissure. In 27 of the 36 cases, the ætiology of the cardiac failure was stated and was in all a condition causing either left-sided or simultaneous left- and right-sided failure, namely aortic valve disease, hypertension, coronary occlusion, and myocardial fibrosis. In accordance with such ætiology, the age incidence is high, 23 of 28 cases being over 40 years.

In 14 of the 36 cases, there was no accompanying effusion in the general pleural cavities. In such circumstances, the correct diagnosis may not be thought of at first because of its rarity. Tuberculous loculated pleural effusion, loculated empyema, or even neoplasm may be wrongly diagnosed. A patient with coronary occlusion, which is a common cause of cardiac interlobar hydrothorax, may have fever, cough, chest pain, and leucocytosis, all of which may suggest empyema.

The cardiac interlobar hydrothorax, however, usually occurs in patients over 40 years of age, when tuberculous effusions are uncommon. The fluid, on examination, has the characteristics of a transudate. A cardiac condition causing left- or simultaneous left- and right-sided failure is present. Radiologically, the fluid is in most cases localized in the right lesser fissure and tends to disappear with treatment of the cardiac failure and to re-appear with relapse; the lung fields tend to show hilar and basal congestion due to associated pulmonary œdema.

Necropsy in some cases of cardiac interlobar hydrothorax—Helm (1917), Steele (1932), Austrian (1932), Levitin (1937), Russakoff and Weinberg (1944)—has shown that fibrous obliteration of the general pleural cavities has left no space other than an interlobar fissure in which the fluid could accumulate.

I wish to thank Dr. W. D. D. Small for permission to publish the case.

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MYXOMA OF HEART WITH NEUROLOGICAL SIGNS

by

PETER MILLS AND MAURICE PHILPOTT

From the Department of Medicine, Lister Hospital, Hitchin, Herts

Myxoma of the heart, although extremely rare, has received a certain amount of attention during the past fifteen years or so, being described by Yater (1931), Gilchrist and Millar (1936), Fawcett and Ward (1939), Thompson (1944), and Burnett and Davidson (1945). The tumour appears to arise always in one or other of the auricles, more often in the left, and the clinical presentation is usually one of progressive, relentless congestive heart failure without previous cardiac symptoms or signs.

The following case is thought to warrant publication, both on the grounds of the rarity of the condition and the fact that, although the final picture was one of congestive heart failure, the case originally presented with neurological symptoms which are unusual in this condition. These symptoms were presumably the result of emboli from the tumour itself or from thrombi forming on its surface. No mention seems to have been made in previous records of this type of presentation, apart from a patient reported by Gorlitzer (1934), who died suddenly; large emboli from a thrombus on the surface of the tumour were found in the cerebral arteries at necropsy, but apparently there had been no neurological signs during life.

Case Report

The patient, a man aged 44 years, was admitted to hospital in August, 1944, in a semi-comatose state. The history from his relations was that he had been vaguely unwell for some four weeks and had become increasingly drowsy two days before admission,

On examination he was found to have a left facial palsy of upper motor neurone type, and a flaccid left hemiplegia with left extensor plantar response. The heart was found to be slightly enlarged to the left, confirmed by radiography, but the sounds were normal and there were no murmurs. His blood pressure was 150/95, and the pulse was regular. The cerebrospinal fluid protein content was 80 mg. per 100 ml., but the fluid was otherwise normal. White blood count, urine, blood urea, and skull X-ray were all normal, and the Wassermann reaction in blood and cerebrospinal fluid was negative. He gradually improved and was discharged from hospital one month after admission. At that time he had only slight weakness in the left limbs, which had now become slightly spastic, the plantar response remaining extensor.

Four months later, in January 1945, the patient was re-admitted owing to a sudden onset of generalized weakness, associated with a confused mental state. The previous day he had collapsed following a hot bath. He now had weakness of the left external rectus, and still had weakness with increased tendon reflexes and an extensor plantar response in the left leg. The left arm now appeared normal, and the facial palsy had recovered. Lumbar puncture still showed 80 mg. per 100 ml. of protein in the cerebrospinal fluid, which was otherwise normal, and the other investigations were still normal. He quickly recovered from the generalized weakness and confused mental state, and was discharged from hospital two weeks later.

He remained well for ten months, and then began to develop shortness of breath and swollen ankles. For this he took to his bed, and, in spite of treatment from his own doctor, progressively got worse. On February 6, 1946, he was again admitted to hospital, and on examination was found to be very cyanosed and orthopnœic, with gross anasarca. The cardiac physical signs were unaltered, and the pulse, although raised in rate to 112, was regular in rhythm. His blood pressure was 140/80. Examination of the central nervous system was as on his previous admission. Treatment with digoxin and mersalyl had no effect, and venesection and paracentesis abdominis gave only a little temporary relief. The patient rapidly became weaker, and the congestion more marked. Some jaundice appeared, owing to hepatic congestion, and he died on February 13, 1946.

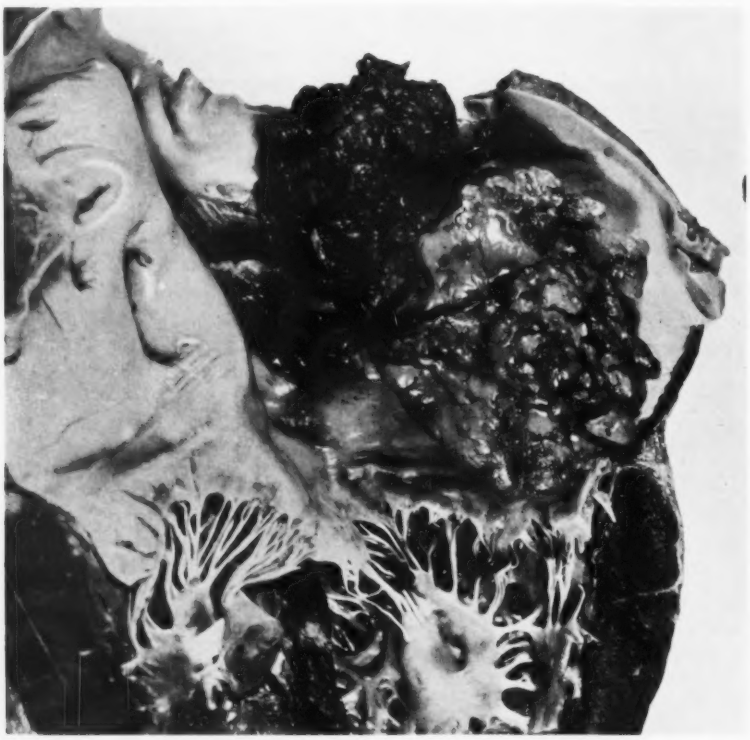

FIG. 1.—The left ventricle and auricle are opened showing the tumour *in situ*: it is attached by a peduncle to the posterior wall of the left auricle.

Necropsy Report

At necropsy the cause of death was found to be heart failure due to blockage of the orifice of the mitral valve by a pedunculated myxoma of the left auricle.

The tumour measured 5 cm. from its attachment to its summit, and 6·5 cm. from above down, and 4 cm. from side to side. It was conspicuously villous. The villi had rounded, smooth tips. The tumour was very gelatinous and grey. Its central part was firmer, the cut surface here being pale yellow. It was attached by an extremely narrow, short pedicle (0·4 cm. diameter, 0·4 cm. long) of tough tissue, to the left auricle 2·3 cm. above the attached border of the posterior cusp of the

mitral valve and 0·7 cm. from the posterior border of the interauricular septum and immediately behind the annulus ovalis.

When the removed heart was held with the apex downward, the lower third of the tumour filled completely the orifice of the mitral valve. Both cusps of the mitral valve and the other three cardiac valves were normal. There was dilatation and hypertrophy of the left auricle (13·5 cm. circumference and 0·35 cm. thickness), and of right ventricle (0·6 cm. thick), and of right auricle. There was no alteration in the left ventricle. The heart weighed 470 g.

Microscopically, sections of the tumour showed very little tissue structure: just a fibrillated matrix with connective tissue cells sparsely scattered, and some areas of necrosis where there were no cells. Collagen fibres could not be demonstrated, and repeated efforts with special stains failed to show the presence of mucin.

In the rest of the necropsy there was pronounced evidence of chronic heart failure—' nutmeg ' liver (weight 1100 g.); hard, dark, red spleen (weight 135 g.); bilateral pleural effusions (1·4 litre each) of straw-coloured fluid; ascites (1·7 litre); and pitting œdema of legs. Both kidneys (weight: left 290 g.; right: 200 g.) showed large sunken white scars of old infarction. The brain showed no macroscopic lesion in numerous sections.

Discussion

The previously recorded cases have been extensively reviewed by Fawcett and Ward (1939), who also described a case of their own, and further cases were described by Thompson (1944), by Burnett and Davidson (1945) and by Brewin (1948). Most of these cases presented with severe congestive heart failure, progressing rapidly and failing to respond to any form of treatment. In such cases the heart usually appeared normal on clinical examination except for disturbed rate. Thompson (1944), however, described a case in which systolic and diastolic murmurs were heard, and Gilchrist and Millar (1936) reported a case with paroxysmal tachycardia.

Hence, although this condition is extremely rare, it might well be borne in mind when one is presented with a case of severe congestive heart failure with no obvious cardiac lesion on clinical examination, especially when the onset has been sudden and the progress rapid, and where the condition fails to respond to treatment. The case here described is unusual in presenting at first with neurological physical signs.

We would like to express our thanks to Dr. Mary Brown of the Pathological department of the Lister Hospital, Hitchin, and to Dr. W. W. Woods of The Bernhard Baron Institute of Pathology, The London Hospital, for their help in the pathological description of this case, and to Mr. John King for the photograph.

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ABSTRACTS OF CARDIOLOGY

Neosynephrine in Treatment of Paroxysmal Supraventricular Tachycardia. W. B. YOUMANS, M. J. GOODMAN, and J. GOULD. *Amer. Heart J.*, **37**, 359–373, March, 1949.

"Neosynephrine" differs from adrenaline in that the molecule has a hydrogen atom instead of a hydroxyl group in the *para* position on the benzene ring. It causes marked hypertension and peripheral vasoconstriction. Its administration is followed by a sinus-inhibition bradycardia. In animals this inhibition may result in a ventricular escape.

The authors studied 19 attacks of paroxysmal supraventricular tachycardia occurring in 9 patients. Up to 2 mg. of neosynephrine was given intravenously during an attack. In only 2 cases, both after major operations, did the rhythm fail to revert to normal. Reversion occurred within 35 to 70 seconds of injection. Unpleasant side effects were few. One case of paroxysmal ventricular tachycardia failed to respond. *A. S. Dixon*

Angiocardiography in Congenital Heart Disease of Cyanotic Type with Pulmonic Stenosis or Atresia. I. Observations on the Tetralogy of Fallot and "Pseudo-Truncus Arteriosus." R. N. COOLEY, H. T. BAHNSON, and C. R. HANLON. *Radiology*, **52**, 329–346, March, 1949.

The authors used angiocardiography in 75 cases of congenital heart disease of the cyanotic type. They employed a modified Robb and Steinberg technique for the injection. The contrast medium was a 70% solution of "diodrast" injected into the basilic vein of the left arm or into the external jugular vein in small children; 140 injections were made without serious reaction.

Nine cases are reported in detail. Seven had the tetralogy of Fallot and 2 had a truncus arteriosus. All were subsequently operated upon, and in one case post-mortem studies were available. An overriding aorta could be demonstrated in all cases. An interventricular septal defect may sometimes be directly demonstrated. Direct visualization of the pulmonary conus is so difficult as to be an untrustworthy guide, but strong presumptive evidence of stenosis may often be obtained. It is not possible by angiocardiography alone to distinguish between pulmonary atresia and a high degree of stenosis. The presence and character of the pulmonary arteries may be reliably determined. Failure to demonstrate the proximal position of the pulmonary artery, however, does not rule out the possibility of a successful anastomosis. *A. Orley*

Cardiac Catheterization in Congenital Heart Disease. By A. COURNAND, M.D., JANET S. BALDWIN, M.D., and A. HIMMELSTEIN. Pp. 108: illustrated. $4.00 or £1 2*s*. New York: The Commonwealth Fund. London: Geoffrey Cumberlege, 1949.

The practical and pioneer contributions of Cournand and his colleagues in applying the technique of cardiac catheterization are well known. This monograph is a detailed study of some cases of congenital heart disease. The first part gives a clear and concise account of the staffing, equipping and technical methods involved in catheterizing the right heart, with a note on its complications. Radiographic observations and tracings of blood pressure recordings taken during catheterization are also illustrated, and formulæ given for calculating blood flow and shunts. The second part of the book consists of a useful selection of seventeen clinical cases illustrating the commoner types of a cyanotic heart disease in which this diagnostic technique has been used. The results are analysed and interpreted in simple language which provides a valuable summary of the scope of this procedure. The volume should serve a useful purpose in emphasizing the highly specialized nature of the investigation of cardiovascular malformations by catheterization. The authors acknowledge these limitations, but in presenting their data so graphically have undoubtedly done service to clinical cardiology. *J. L. Lovibond*

Aspiration of Blood from Pericardium in Treatment of Acute Cardiac Tamponade after Injury. Further Experience, with Report of Cases. M. M. RAVITCH and A. BLALOCK. *Archives of Surgery*, **58**, 463–477, April, 1949. 4 figs.

Despite the lowered operative mortality rate during the last 5 years in the treatment of wounds of the heart, the authors reaffirm their opinion, first expressed in 1943, giving preference to the more conservative pericardial aspiration for hæmopericardium causing tamponade, and reserving cardiorrhaphy for those patients in whom bleeding continues or is resumed after aspiration.

In a further series of 10 cases manifesting signs of tamponade careful records are supplemented by illustrative charts of progress. Eight patients were successfully treated by aspiration, one was subjected to immediate cardiorrhaphy, and the other to operation after two aspirations. All survived without complications.

C. A. Jackson

Clinical Auscultation of the Heart. By S. A. LEVINE, and W. P. HARVEY, (W. B. Saunders Company—Philadelphia and London). Price 32*s.* 6*d.* Pages 327.

The authors have been impressed by the reluctance of many modern clinicians to make full use of the stethoscope, and find the availability of more complicated, and perhaps more impressive apparatus for the investigation of cardiovascular disorders tending to supplant the simpler method of auscultation by the stethoscope. Auscultation may be a small part of the total assessment of cardiac function yet it is a very important and often a very simple one. The value of this book lies not so much in its lucid exposition of phonocardiology, amply illustrated by excellent photographic reproductions, as in the co-relation of these instrumentally obtained records with clinical auscultatory findings. The work contains much common sense, practical observation, and good teaching that will profit all clinicians; its appearance is the more acceptable at a time when the study of heart sounds and murmurs is the subject of renewed interest.

J. L. Lovibond

Coagulation, Thrombosis, and Dicumarol. SHEPARD SHAPIRO, M.D. and MURRAY WEINER B.S.M.S., M.D., Brooklyn Medical Press, New York. 1949. Price $5.50.

The discovery and synthesis of dicumarol by Link and co-workers placed a powerful weapon in clinicians hands to combat thrombosis. The senior author of this monograph was closely associated with Link's group when the question of using this new drug in man was considered: the present work is based largely on the results of their investigations in this field.

The chapters on the relationship between decreased coagulability, low prothrombin, and hæmorrhagic phenomena are valuable. That hæmorrhages may occur when the coagulability of the blood or its prothrombin content are but little altered should be recognized. Furthermore, the control of such drugs needs the closest collaboration between clinician and pathologist. The so-called " prothrombin time " estimation is not a measure of one substance but rather of the behaviour of a complex of reactions occurring simultaneously under more or less standard conditions. The relation between prothrombin activity and vitamin K is very clearly expressed, especially in the presence of liver disease. Salicylates potentiate to a marked degree the lowering of prothrombin by dicumarol.

There is a clear discussion on the dose and control of the drug in which the authors give their reasons for preferring the " intermittent dosage " method by which a dose large enough to guarantee a therapeutically effective prothrombin time prolongation is given at the onset. No more is given until the prothrombin time tends towards the normal. This method is claimed to be safer than the " daily dose " method. Each case must be the subject of individual attention; general rules of dosage are not practicable.

There is an interesting chapter on the estimation of dicumarol in plasma and body fluids. It would appear to be excreted by the large bowel, since the drug does not appear in bile or urine.

The chief criticism of this work is that it is the representation of one group and that the views of other and conflicting schools are hardly represented at all. Furthermore, the authors have apparently completely misunderstood the two-stage prothrombin procedure. This monograph is of a high order in production.

J. G. Humble

Some Effects of Digoxin upon the Heart and Circulation in Man. Digoxin in Chronic Cor Pulmonale. M. I. FERRER, R. M. HARVEY, R. T. CATHCART, C. A. WEBSTER, D. W. RICHARDS, and A. COURNAND. *Circulation*, **1**, 161–186, 1950. 7 figs., 13 refs.

Intravenous administration of digoxin in doses of 1 to 1·5 mg. caused a rise in cardiac output, a rise in pulmonary artery pressure, a fall in right ventricular and diastolic pressure, and a fall in venous filling pressure in 5 cases of chronic anoxic cor pulmonale with the clinical features of congestive heart failure. A parallel study was made on 3 cases of chronic cor pulmonale and 2 cases of pulmonary hypertension in which there was no evidence of heart failure: in these the effect of intravenous digoxin was negligible. The authors feel that digoxin may well have caused these effects by a direct action on the cardiac muscle, but admit that they were unable to exclude a primary vasodilator action.

When, as a result of medical treatment (rest in bed, digitalization, administration of mercurial diuretics to 2 patients, and antispasmodic inhalations) clinical improvement was obvious, there was a marked increase in arterial oxygen saturation, vital capacity, and maximum ventilation, accompanied by a conspicuous reduction in cardiac output, pulmonary artery pressure, and right ventricular diastolic pressure—indeed, the pulmonary artery pressure in 4 of the patients became almost normal.

The reversibility of chronic cor pulmonale is stressed.

Paul Wood

The Cardiac Output in Normal Pregnancy as Determined by the Cournand Right Heart Catheterization Technique. H. F. H. HAMILTON. *J. Obstet. Gynaec. Brit. Emp.*, **56**, 548–552, 1949. 1 fig., 10 refs.

The cardiac output was determined in a series of 32 non-pregnant women in the child-bearing age and in 75 normal women in various stages of pregnancy. The technique of cardiac catheterization used was similar to that used by Cournand in 1945. In 24 normal non-pregnant women the mean cardiac output was 4·5 litres a minute and the cardiac index was 3 litres a minute. There were 68 successful estimations in pregnant women, whose output began to rise between the 10th and 13th weeks and reached its maximum around the 7th month with an average of 5·7 litres a minute. Following this there was a steady fall until the 40th week when the output was 4·6 litres a minute. The oxygen consumption during pregnancy rose steadily to 251 ml. a minute, compared with an initial value of 211 ml. a minute.

The fact that the cardiac output returns to normal

before the onset of labour is of clinical interest. The work of the heart has decreased during the last weeks of pregnancy and by term it is under optimal conditions to deal with the sudden changes which occur throughout labour, particularly in the third stage. The benefit of this to a patient with a diseased heart is obvious.

[It would seem from this article that the present practice of many obstetricians of inducing premature labour in cases of heart disease is not sound physiologically; the outlook for the patient would be better if the pregnancy was allowed to go to term.] *B. G. Spiers*

Effect of Auricular Fibrillation on the Coronary Blood Flow. R. WÉGRIA, R. P. KEATING, H. P. WARD, F. DREYFUSS, C. W. FRANK, and M. R. BLUMENTHAL. *Amer. J. Physiol.*, **160,** 177–182, Jan., 1950. 3 figs.

Direct measurements of the arterial blood pressure and the blood flow in the coronary circulation were made in 16 dogs under sodium barbitone anæsthesia, and auricular fibrillation was induced by electrical stimulation of one of the auricular appendages. At the onset of fibrillation there was a marked fall in blood pressure and coronary flow. Within a few seconds both blood pressure and coronary blood flow returned towards their original levels and, if fibrillation persisted long enough, rose temporarily above initial values. A similar observation was made at the end of fibrillation, the coronary flow especially rising above control level; both values then decreased progressively, the blood pressure being first to reach its control level. The authors discuss the mechanism and significance of the cardiovascular reactions responsible for the observed phenomena.

[From the clinician's point of view the experimental finding that an attack of auricular fibrillation with a high ventricular rate calls for an increase in coronary blood flow is of great importance. It explains the cause of heart failure in a subject with fibrillation and coronary sclerosis in whom an " increase (in coronary flow) may be neither possible nor sufficient to meet the demands."] *A. I. Suchett-Kaye*

Treatment of Paroxysmal Supraventricular Tachycardia with Lanatoside C. J. G. BARROW. *Ann. intern. Med.*, **32,** 116–119, Jan., 1950.

Lanatoside C is, in the author's opinion, the most effective drug for treatment of an acute attack of paroxysmal supraventricular tachycardia (although it may have to give place to " neosynephrine "). It is non-toxic and quite safe, and is stated to be highly efficacious quickly and almost invariably. It must never be given without electrocardiographic identification of the arrhythmia, and it is contra-indicated in any form of ventricular rhythm. Furthermore, it has little value as a preventive, being far inferior to quinine or digitalis in that respect. The dose is 1 mg. intravenously, repeated if necessary. *G. F. Walker*

Atrophy of the Heart: A Correlative Study of Eighty-Five Proved Cases. H. K. HELLERSTEIN and D. SANTIAGO-STEVENSON. *Circulation*, **1,** 93–126, Jan., 1950. 17 figs., bibliography.

Cardiac Changes in Childhood Tuberculosis. V. M. AFANASEVA. *Arkh. patol.*, No. 4, 52–61, 1949. 5 figs., 19 refs.

Tuberculous myocarditis is usually regarded as an uncommon complication of generalized tuberculosis, and lesions are seldom seen with the naked eye. Non-specific inflammation has been reported much more frequently. In order to re-examine this question, 118 hearts of children dying of tuberculosis were studied with considerable care. Macroscopical tuberculous lesions were found in only 2 cases. Non-specific lesions were common and included perivascular œdema, fibrinoid degeneration and necrosis of vessels, hæmorrhage, and perivascular cellular infiltration. In contrast to some previous findings, there was not a single example in this series of lesions resembling the Aschoff bodies. Fifty cases in which diffuse or focal cellular infiltration was found were studied further by means of serial sections. This revealed a surprisingly high proportion of specific tuberculous lesions: 26 out of the 50, or 22% of the total. Tubercle bacilli were found in only 4 cases. *L. Crome*

The Atrophic Kidney and Hypertension. J. R. KILMAN, E. O. BRADFIELD, and C. M. SIMPSON. *J. Urol*, **62,** 417–425, 1949. 8 refs.

Since Butler reported in 1937 the apparent cure of hypertension by removal of a diseased kidney many cases have been recorded which confirm the fact that nephrectomy may relieve hypertension if the kidney is diseased. The authors report 13 cases of unilateral atrophic pyelonephritis treated by nephrectomy for this purpose. In 7 cases the blood pressure returned to normal and has remained normal for 2 to 9 years. In 5 cases the blood pressure remained the same; 3 of the patients died, after 6 months, 9 months, and 4 years respectively. In one case the blood pressure was still unchanged after 18 months, though the symptoms were relieved. The average age in this group of patients was 28 years. In 6 of the 7 cases with good results the opposite kidney was considered to be hypertrophied, while this was not noted in any case in which results were poor. The authors believe that in patients selected for nephrectomy to relieve hypertension: (1) the affected kidney should show a definite reduction in function; (2) the normal kidney should be hypertrophied, indicating that there is compensation for loss of function in the diseased kidney; (3) the best results can be expected in patients below 45 years of age. *J. E. Semple*

Surgical Treatment of Constrictive Valvular Disease of the Heart. H. G. SMITHY, J. A. BOONE, and J. M. STALLWORTH. *Surg. Gynec. Obstet.*, **90,** 175–192, 1950. 13 figs., 19 refs.

The authors review the history of attempts made to treat valvular stenoses of the heart surgically. They have now operated upon 7 patients for mitral stenosis, and describe the technique of both the transventricular and transauricular procedure which they used. [The original paper should be consulted for the details.] They

discuss the pros and cons of the two approaches, and favour the transventricular method. Two of their patients died. Of the remainder none was made worse, and 4 were improved.

During operation marked arrhythmia of the heart was observed during the displacement of the apex despite the topical application of procaine, but after rest and infiltration of the ventricular muscle with local analgesic further manipulations caused little disturbance. Irregularities were less common when the transauricular route was used.

They discuss the selection of patients for operation, saying that those with evidence of congestive failure should not be operated upon and that the ideal candidates are those suffering from the mechanical effects of the lesion only, without associated myocardial damage. They are of the opinion that in these patients the creation of a valvular incompetence by operation is well borne.

J .R. Belcher

The Retinal Vessels in Hypertension. A. LEATHAM. *Quart. J. Med.*, **18,** 203–215, 1949. 8 figs., 27 refs.

The retinal arteries were studied in 111 cases of hypertension and in 103 controls. Changes in the retinal arteries indicative of hypertension consist of irregularity of the lumen, generalized narrowing (the healthy artery is normally two-thirds the width of its companion vein), pallor of the arteriolar blood column, changes at arteriovenous crossings, and a broadened or exaggerated light reflex. It is suggested that these arterioles should be called hypertensive retinal arterioles.

Changes in the retinal arterioles were much commoner in subjects with a diastolic blood pressure of 110 mm. Hg or over than in those with a raised systolic pressure and a normal diastolic pressure. Radiological evidence of enlargement of the left ventricle and electrocardiographic evidence of left ventricular preponderance were commonly associated with the presence of hypertensive retinal arterioles. *Geoffrey McComas*

The Femoral Pulse Curve in Coarctation of the Aorta. S. BJORK and K. LIEDHOLM. *Acta med. scand.*, **136,** 97–104, 1949. 5 figs.

Femoral and carotid pulse tracings in 3 patients with aortic coarctation were compared with those in 10 normal subjects. The femoral pulse curve of these patients was considered pathognomonic of aortic coarctation in three respects: firstly, the peak of the curve was reached much later than in normal subjects; secondly, this same peak occurred after the end of cardiac systole recorded in the carotid pulse curve, whereas in normal subjects it occurs before the end of systole; thirdly, the descending limb of the curve fell more slowly than in normal subjects and contained no secondary peak. *A. Wynn Williams*

Interatrial Septal Defect. R. S. COSBY and G. C. GRIFFITH. *Amer. Heart J.*, **38,** 80–89, 1949. 14 refs.

This is a short review of the present knowledge of interatrial septal defect and includes tabular presentations of (1) the symptoms and signs in 16 patients with clinical evidence of atrial septal defect, and (2) the pathological findings in a further 19 cases that came to necropsy. No case reports are given. Special attention is called to the sometimes enormous enlargement of the right ventricle. The systolic murmurs which may occur are listed. An associated apical diastolic murmur (in 2 of 16 cases) indicates the presence of mitral stenosis (Lutembacher's syndrome) [but no explanation is given of the frequent pulmonary diastolic murmur (in 7 of 16 cases) associated with marked cardiac enlargement]. Radiological findings are described and their frequency listed. Prominence of the pulmonary artery was constant and sometimes extreme. Pulmonary artery pulsation was present in some cases and was most easily seen on the right side.

The intravenous ether circulation time may give diagnostic information. Some ether may be shunted through the septal defect and, by-passing the lungs, cause a wave of paræsthesiæ over the body, which occurs after the same interval as the arm-to-lung circulation time. Angiocardiography is of little diagnostic value, but cardiac catheterization during fluoroscopy may provide proof of the existence of a defect. *A. S. Dixon*

Defect of the Ventricular Septum. Summary of Twelve Cases and Review of the Literature. A. SELZER. *Arch. intern. Med.*, **84,** 798–823, 1949. 1 fig., bibliography.

A description is given of 12 cases of uncomplicated ventricular septal defect (*maladie de Roger*), together with necropsy findings, and 80 reported cases are reviewed. The following conclusions are reached: (1) The great majority of defects are located between the membranous and the anterior muscular septum, involving both and connecting the sub-aortic area of the left ventricle with the right ventricle immediately in front of the median leaflet of the tricuspid valve. This position is similar to that of the defect in the tetrad of Fallot and in Eisenmenger's complex. In a small minority the defect is lower down the septum. (2) Large defects were usually found in infants and were uncommon in those over 15 years of age. The effect upon the circulation depended upon the size of the defect. If large, the signs were similar to those of atrial septal defect or patent ductus arteriosus, with hypertrophy of the right ventricle and enlargement of the pulmonary artery and its branches. (3) The shunt in an average case of ventricular septal defect is from left to right. It is suggested that those with cyanosis should be regarded as examples of the Eisenmenger complex and that it may be difficult to decide at necropsy whether a minor grade of over-riding of the aorta is present. (4) Much evidence is presented in favour of the view that transposition, Fallot's tetrad, Eisenmenger's complex, and ventricular septal defect have a common ætiology in incomplete detorsion of the primitive tube, ventricular septal defect being the least severe grade. (5) In most cases the classical harsh systolic murmur, with thrill, was present in the 4th interspace. In 5 out of 70 cases no murmur was audible, and in one case a diastolic murmur only. No correlation could be found between the size of the

defect and the type of the murmur. Early diastolic murmurs, possibly due to pulmonary incompetence, were not infrequently present in addition to the harsh systolic bruit. (6) The prognosis depends upon the size of the defect. There is also the well-known high susceptibility to bacterial endocarditis. *C. W. C. Bain*

Studies of Congenital Heart Disease. IV. Uncomplicated Pulmonic Stenosis. J. W. Dow, H. D. Levine, M. Elkin, F. W. Haynes, H. K. Hellems, J. W. Whittenberger, B. G. Ferris, W. T. Goodale, W. P. Harvey, E. C. Eppinger, and L. Dexter. *Circulation*, **1**, 267–287, Feb., 1950. 5 figs., 49 refs.

Eight cases of simple pulmonary stenosis are reported with clinical, radiological, and electrocardiographic findings and a description of the circulatory dynamics as determined by means of cardiac catheterization. Angiocardiography was not carried out. There were 6 males and 2 females, aged 11 to 26. None was cyanosed; 3 were symptom-free, and 3 had slight effort intolerance and 2 moderate breathlessness on exertion. They were all normally developed. The systolic thrill and murmur were maximal in the 2nd, 3rd, or 4th left intercostal space. The pulmonary second sound was sometimes normal, but sometimes decreased or increased in intensity. The pulmonary arc was prominent in 6 cases, but the peripheral pulmonary vascular markings were normal. The " P pulmonale " in leads II and III was seen in only one instance. Late electrical activation of the right ventricle due to right ventricular hypertrophy or slight incomplete right bundle-branch block occurred in 5 cases.

In all cases the pulmonary artery pressure was appreciably lower than that in the right ventricle. The arterial oxygen saturation was normal. Samples from the superior vena cava, right auricle, right ventricle, and pulmonary artery were essentially similar. Ventilation, oxygen consumption, arterio-venous oxygen difference, cardiac output, and cardiac indices were similar to those in normal controls.

Responses to effort remained normal at the expense of a considerable rise in right ventricular pressure.

[This article contains a valuable review of the literature.] *Paul Wood*

Congenital Pulmonary Stenosis with Closed Ventricular Septum. K. D. Allanby and M. Campbell. *Guy's Hosp. Rep.*, **98**, 18–53, 1949. 29 figs., 25 refs.

It is often stated that pulmonary stenosis with a closed ventricular septum is an uncommon cardiac anomaly: 8 cases are here reported, 7 of them verified at necropsy. The pulmonary stenosis in such cases is of the valvular type, the cusps being fused to form a cupola with an aperture of varying size at its centre. The clinical course is determined by the severity of the stenosis and by the presence or absence of a patent foramen ovale. Ordinarily there are few symptoms other than some degree of dyspnœa until the late teens or early twenties. At this time a mounting pressure in the right side of the heart may make a potentially patent foramen ovale permeable and so allow a shunt from right to left to take place. Cyanosis then appears and gradually intensifies, with increasing disability of the subject. If the foramen ovale is sealed, the patient is acyanotic, but ultimately there may be peripheral cyanosis due to increased utilization of oxygen and possible interference with adequate oxygenation in the lungs. There is a harsh systolic murmur, with or without a thrill, in the 2nd left interspace, while the pulmonary second sound is diminished or absent. The electrocardiogram usually shows right axis deviation, with large, pointed P waves in lead II.

The authors point out that, in this as in other congenital abnormalities such as coarctation, the size of the stenotic pulmonary orifice does not increase in relation to the increasing size of the heart and pulmonary artery, and thus becomes of greater importance as the patient grows. Further, as in other obstructive lesions, the valvular stenosis provides a site for infective processes or increased fibrosis and stenosis.

[This is an important contribution to the study of an abnormality which has so far received little attention, and the original paper should be consulted.]

James W. Brown

Genetic and Environmental Factors in Congenital Heart Disease. M. Campbell. *Quart. J. Med.*, **18**, 379–391, 1949. 21 refs.

After reviewing the literature the author reports personal observations based on over 300 case notes of children with congenital heart disease. About 250 of these were cyanotic and 50 acyanotic; 185 were boys and 155 girls. The only environmental factor of importance found was maternal rubella during the first 2 or 3 months of pregnancy; this was present in 4 cases (1·6% of the cyanotic group). Genetic factors proved to be far more important than environmental ones. This view was supported by the observations that more congenital defects were present amongst the sibs and more distant relatives of these patients than could be expected as the result of chance; moreover, congenital defects in other parts of the body were found in many cases. Several instances of congenital heart disease occurring in a family were encountered, two of them striking; these are described in some detail. Although the causes of congenital heart disease are mainly genetic the risk that the next 2 or 3 children will show any serious congenital defect is so small that it is justifiable to reassure the mother on this account. *A. Schott*

The Differentiation of Mediastinal Tumour and Aneurysm: Value of Angiocardiography. I. Steinberg and C. T. Dotter. *Brit. J. Radiol.*, **22**, 567–572, 1949. 12 figs., 9 refs.

The authors stress the importance of accurate preoperative diagnosis of mediastinal masses, mentioning tumours in which pulsation is transmitted and aneurysms that do not pulsate because of the thickness of their walls or the presence of clot. In 1948, angiocardiographic examinations were carried out in 238 cases.

The apparatus used was simple and consisted of a standard stereo cassette changer permitting the taking of 2 films per injection of opaque medium.

G. A. Stevenson

Healed Subacute Bacterial Endocarditis, a New Entity. S. R. KAPLAN, R. H. ROSENMAN, L. N. KATZ, and W. A. BRAMS. *J. Amer. med. Ass.*, **141,** 114–116, 1949. 21 refs.

The authors report their observations on 18 cases of subacute bacterial endocarditis treated by intensive administration of pencillin and followed up for periods varying from 25 to 61 months. The causative organism in all but one case was *Streptococcus viridans*, the exception being a β-hæmolytic streptococcus.

In 6 patients who had dynamically significant aortic insufficiency investigation revealed progressive cardiac failure: two of these died within a year and one of them 3 years later. The remaining 12 patients, none of whom had severe aortic insufficiency, remained well. The authors therefore conclude that gross aortic regurgitation is of grave significance. In their study no correlation was observed between progressive cardiac disability following cure of infection and age, sex, duration of illness before treatment, length of hospital stay, or total penicillin dosage. The authors contend that penicillin, besides being bactericidal, influences the healing process, checks the thrombo-embolic "showers," and thus reduces the incidence of cardiac insufficiency.

S. Karani

Occurrence and Prognostic Significance of Gallop Rhythm. J. FROST. *Acta med. scand.*, **134,** 153–170, 1949. 25 refs.

This investigation was carried out on 6000 adult patients, of whom 57 were examined by phonocardiography. The added sounds in every instance were left-sided and occurred during diastole only. In healthy subjects the physiological third heart sounds were noted less frequently with advancing age.

Gallop rhythm was present in 44% of patients with coronary thrombosis and in 17% of those with arteriosclerosis and hypertension; in all of these the mortality rate was higher and survival time shorter than in those without gallop rhythm. There was also a greater incidence of abnormal electrocardiograms, left bundle-branch block and abnormal T waves in lead I being particularly common. Gallop rhythm was also present in 15% of patients with affections of the aorta and aortic valve; again the prognosis was worse than in those without the added sounds. Gallop rhythm associated with rapid filling appeared to have a worse significance than either the auricular or the summation type.

Gallop rhythm was noted in patients with beri-beri and traumatic heart disease but was seldom present with mitral stenosis or thyrotoxicosis. In cases of congenital heart disease and constrictive pericarditis gallop rhythm was sometimes observed but in these younger patients difficulty was found in differentiating the added sounds from the normal third heart sounds.

The author's conclusion is that gallop rhythm is a sign of lowered functional capacity of the heart, indicative of a bad prognosis; its importance lies in the frequent association with other adverse signs such as cardiac enlargement and serious electrocardiographic abnormalities.

Winston M. L. Turner

A Re-evaluation of Papaverine in the Treatment of Angina Pectoris. A. J. SIMON, N. DOLGIN, A. J. L. SOLWAY, J. HIRSCHMANN, and L. N. KATZ. *J. Lab. clin. Med.*, **34,** 992–997, 1949. 13 refs.

The effect of the oral administration of papaverine on the anginal attacks of 13 patients was observed in a carefully controlled series of experiments. In doses of 400 to 800 mg. daily it did not significantly reduce the number of attacks, except in two cases. In one of these the effect was ascribed to the sedative effect of the drug, and its mode of action in the other case was uncertain. Constipation and drowsiness were noticed as the most common toxic effects. This careful re-evaluation of the use of oral papaverine in the treatment of the anginal syndrome leads the authors to conclude that it is of limited value.

H. E. Holling

Infarction of the Interventricular Septum. D. LITTMANN. *New Engl. J. Med.*, **241,** 89–94, 1949. 5 figs., 1 ref.

The most frequent electrocardiographic sign in infarction of the interventricular septum (apart from those indicative of any cardiac infarction) is that of impaired interventricular conduction or frank bundle branch block. Less commonly the Roesler and Dressler pattern is noted (posterior infarction pattern in standard limb leads with anteroseptal pattern in præcordial leads), and still less frequently the picture of uncomplicated myocardial infarction. In this series of 11 fatal cases, the pattern of simple infarction was always that of infarction of the posterior wall. With combined anterior-wall and septal involvement, bundle branch block was invariably found and was accompanied in 2 cases by A-V dissociation. Bundle branch block is not certain evidence of septal involvement in myocardial infarction and, conversely, septal infarction may occur without definite electrocardiographic evidence. Mortality in septal infarction is high, probably about 70% and, this may well be related to the frequency of arrhythmia and interference with conduction.

T. Semple

Studies on the Circulation of Blood in Man. VI. The Pulmonary Capillary Venous Pressure Pulse in Man. H. LAGERLÖF and L. WERKÖ. *Scand. J. clin. Lab. Invest.*, **1,** 147–161, 1949. 14 figs., 9 refs.

There is no significant anastomosis between the smaller branches of the pulmonary artery, for, if a cardiac catheter is pushed along the pulmonary artery of the living subject until it obstructs a fine branch, fully oxygenated blood may be withdrawn. If the catheter is filled with fluid and attached to a manometer, the pressure recorded is that of the pulmonary capillaries and veins (p.c.v.).

The authors used this method to obtain pulse-pressure

tracings of the p.c.v. in 50 subjects, including normal persons, pregnant women, and patients with hypertension, mitral valve disease, pulmonary emphysema, and auricular septal defect. They conclude that the mean p.c.v. pressure is about 2 mm. Hg higher than the left auricular mean pressure, which in turn is higher than the right auricular mean pressure. The pulmonary capillary pressure may be elevated above the colloid osmotic pressure of the plasma during left ventricular failure, thus affording a mechanical explanation for pulmonary œdema. Mitral stenosis is indicated in the p.c.v. tracing by an abnormally high auricular pressure wave; mitral incompetence by an unusually early and high systolic pressure rise.

[Many tracings are reproduced relating the p.c.v. pressure waves with those in other parts of the heart and pulmonary circulation, and with phonocardiographic records. This article should be studied in the original by those interested.] *Martin Hynes*

The Effect of Body Position and Reference Level on the Determination of Venous and Right Auricular Pressure. J. O. DAVIES and N. W. SHOCK. *Amer. J. med. Sci.*, **218,** 281–290, 1949. 3 figs., 12 refs.

Ten subjects were studied; of these 3 were in congestive heart failure and one had a superior caval obstruction.

Technique is given in detail. [Those interested should consult the original paper.] There was no statistical difference between the recordings on the different instruments, nor did the venous pressure in the supine position differ significantly before and after tilting to the 45-degree position. Antecubital venous pressure increased with the assumption of a 45-degree sitting posture. The increase was from approximately 110 to 150 mm. saline. These results differ from those of Burch and his associates, who reported no such change. *A. T. Macqueen*

Comparison of the Constant and Instantaneous Injection Techniques for Determining Cardiac Output. W. T. RASHKIND and J. H. MORTON. *Amer. J. Physiol.*, **159,** 389–393, 1949. 3 figs., 5 refs.

Mechanism of the Auricular Arrhythmias. M. PRINZMETAL, E. CORDAY, I. C. BRILL, A. L. SELLERS, R. W. OBLATH, W. A. FLIEG, and H. E. KRUGER. *Circulation*, **1,** 241–245, 1950. 3 refs.

The mechanisms of the four auricular arrhythmias, namely, premature beats, paroxysmal tachycardia, auricular flutter, and auricular fibrillation, induced by the aconitine and post-electrical-stimulation methods, have been investigated in more than 200 dogs by means of high-speed cinematography, cathode-ray oscillography, and multiple-channel electrocardiography. Films of the auricles of the intact, exposed heart were taken in colour at speeds of 2000 frames a second, the motion of the auricles being slowed 250 times when the films were subsequently projected at 8 frames a second; auricular events that had originally occupied one second thus took 4 minutes to view on the screen. A magnifying lens was used which enlarged the image of the auricle 100 or more times on projection, and by means of such pictures the auricular contraction wave could be seen for the first time.

Auricular fibrillation was seen to be characterized by two phenomena: (1) Minute, irregular contractions which were continuously present. These were termed " M " contractions and involved an area of auricular wall approximately 0·03 to 3 mm. in diameter. (2) Large, rhythmic, wave-like contractions, termed " L " contractions, which swept across the auricle at a rate of 400 to 600 a minute, showing no sign of pursuing a circus path. In the ordinary electrocardiogram the familiar " f " waves probably represent the L contractions, and the M contractions are probably responsible for the tiny, rough irregularities on the " f " waves. It was concluded " that in both man and animals auricular fibrillation is a chaotic heterorhythmic disturbance," and that Lewis's hypothesis that a circus movement is present which gives rise to daughter waves is erroneous. Similarly, no evidence of a circus movement was found in the film records of auricular flutter, the flutter waves being similar to the L waves of auricular fibrillation, but more regular and generally more vigorous, originating at the point of local application of aconitine and spreading thence in all directions at once. The appearances in paroxysmal auricular tachycardia were essentially similar to those in auricular flutter, the only differences being (1) that the auricular rate in paroxysmal tachycardia was slower than in flutter and, consequently, each auricular wave was followed by a ventricular response (that is to say, there was no auriculo-ventricular block); and (2) in paroxysmal tachycardia the propagation of the individual waves was faster than that of the flutter waves.

The present conception of the action of anti-arrhythmic drugs such as quinidine and digitalis, namely, that they act largely through their supposed effect on the gap between the head and tail of the circus movement, becomes untenable in the light of these observations.

S. Oram

Auricular Fibrillation in Normal Hearts. H. H. HANSON and D. I. RUTLEDGE. *New Engl. Med.*, **240,** 947–953, 1949. 27 refs.

Auricular fibrillation is not always associated with organic heart disease, as was recognized as far back as 1911 by Mackenzie. The authors have reviewed 30 such cases, in patients who have been followed-up for periods ranging from 2 to 46 years, out of a total of 651 cases of auricular fibrillation seen at the Lahey Clinic, Boston, over a period of 20 years. In some of them the condition was paroxysmal and attacks might cease after some time; in others the condition remained persistent. It is pointed out that when the patient dies of other disease the heart shows no anatomical or histological abnormality. In ætiology, reflex autonomic activity would appear to play some part. The duration and frequency of paroxysms was unpredictable. If the patients survive sufficiently long the incidence among them of coronary disease, hypertensive heart disease, or other conditions is comparable to that in those of the population with previously normal hearts. There seems to be no

tendency to thrombus formation or subsequent embolism; the latter manifestation probably results from circulatory failure with dilatation of the auricles rather than auricular fibrillation without failure. This form of auricular fibrillation is probably much commoner than is generally recognized owing to the absence of symptoms.

In treatment the important thing is to watch the ventricular rate. As long as this remains at a reasonable level there is no need for any drug therapy. Quinidine may restore normal rhythm but the authors consider that even the very small risk of toxic effects may make its use undesirable. One patient in this series had been taking a maintenance dose of quinidine for 16 years and attacks still occurred whenever the drug was discontinued. *J. McMichael*

Congenital Malformations of the Heart. HELEN B. TAUSSIG, New York: The Commonwealth Fund. London: Geoffrey Cumberlege. (Pp. 618; 46 plates; 177 figs. £2 15*s*.)

With advancing experience in the special techniques of cardiac catheterization, gas analyses and angiocardiography, attention may be focussed away from the clinical aspect of diagnosis in congenital heart disease. But let this not detract from Dr. Taussig's book with its clear presentation and argument, the value of which is, indeed, enhanced by emphasis on the problem from the clinical angle. Her diagnostic interpretation of the deformed heart is made from the study of its functional capacity and anatomy, basing this on clinical and radioscopic assessment alone. The book is illustrated by excellent diagrams and X-rays which greatly simplify the text of her argument. Since her results are mainly derived from personal experience and observation, she admits to an incomplete bibliography. This will doubtless be remedied in her next edition, already inevitable, to embrace the immense advances in knowledge which surgical treatment has latterly brought about, and to satisfy the demand from those many workers in this field. *J. L. Lovibond*

Diseases of the Heart. CHARLES K. FRIEDBERG, M.D., Associate Physican, Mount Sinai Hospital, New York; Lecturer in Medicine, Columbia University. Philadelphia and London: W. B. Saunders Company. Price 57*s*. 6*d*.

This is a most complete modern textbook. It covers the recent advances in cardiology and emphasises the physiological background to clinical disorders of the heart. Special discussion is devoted to cardiac output, blood volume, extracellular fluids, blood oxygen concentration, intracardiac pressures and blood flow, and to demonstrating the growing practical importance of these quantitive measurements and their application to every day diagnosis and treatment in clinical cardiology. Circulatory failure, surgical advances, angiocardiography, and the newer knowledge of electrocardiography and other graphic methods such as electrokymography, are given full recognition and are lucidly described. The work is remarkable for its completeness and is noteworthy for the rich lists of references which follow each chapter. The exhaustive scientific and clinical literature has been most thoroughly covered and the bibliography is quite up-to-date. The volume will, therefore, serve a large field of readers; both teachers and students alike will benefit from its pages. The style is clear and concise and its presentation assimilable. Perhaps the radiograms could be bettered in subsequent editions. *J. L. Lovibond*

A Manual of Cardiology. THOMAS J. DRY, Second Edition. Published by W. B. Saunders Company, Philadelphia and London. Price 25*s*.

The deserving popularity of this small book by the Associate Professor of Medicine, Minnesota University, is the basis for a second edition within seven years of its first appearance. The author's commendable clarity of description and the general arrangement of his text make it much more than a synopsis of the subject. In a work of this sort, it is difficult not to be dogmatic, indeed, the authority of some of his descriptions adds to their value, such as that of the thyrotoxic patient "who looks stimulated;" some readers might disagree with his statement that "the more effort it takes to produce anginal pain the better is the prognosis, regardless of the pathologic condition causing such coronary insufficiency." The chapter on congenital heart disease is clear and helpful, but in "the diagnostic features of the more important congenital anomalies" it is surprising to find a whole page devoted to mitral atresia, a rare condition. The subject of electrocardiography in relation to clinical problems is both comprehensive and readable, though his explanation of the pattern common in obesity is not one that is generally accepted. Emphasis on the fundamental considerations of the normal heart, and evidence of the writer's sane yet critical clinical balance, are prominent throughout this up-to-date book. *J. L. Lovibond*

Modification of the Cardiac Output after Intravenous Injection of Hypertonic Glucose Solution. M. SEGERS and J. P. WALSH. *Amer. J. med. Sci.*, **217**, 494–497, May, 1949.

A single intravenous injection of 50 ml. of hypertonic glucose solution (50%) was found to produce an increase in the cardiac output to 10 to 30% above the control figure in normal persons and those with cardiac disease. In normal subjects this augmentation was temporary; in the patients it was much more prolonged. The determinations of cardiac output were made by the ballistocardiographic method of Starr (*J. clin. Invest.*, 1940, **29**, 437). *A. I. Suchett-Kaye*

On the Mechanism by Which Intravenous Injections of Hypertonic Glucose Solution Cause Increased Cardiac Output. J. P. WALSH. *Amer. J. med. Sci.*, **217**, 498–504, May, 1949.

The results of experiments on normal subjects and patients with heart disease seem to show that increased filling of the heart is not the operating factor in increasing the cardiac output, since, although there was a significant

rise in circulating blood volume after injection of hypertonic glucose, the rise in venous pressure was "almost neligible." In the absence of evidence that other factors are involved, the author assumes that glucose has a specific stimulating action on the myocardium, as the rise in blood glucose level after injection could be constantly correlated with the increase in cardiac output. It was also noted that glucose had a more lasting effect on diseased than healthy cardiac muscle.

A. I. Suchett-Kaye

Treatment of Heart and Kidney Disease and of Hypertensive and Arteriosclerotic Vascular Disease with the Rice Diet. W. KEMPNER. *Ann. intern. Med.*, **31**, 821–856, Nov., 1949.

Benign hypertensive vascular disease can be effectively treated by the rice diet even when critical complications are present, and malignant hypertension may be greatly improved. Of 777 cases thus treated over 70% were benefited as judged by one of the following effects: decrease in the sum of systolic and diastolic pressures by at least 40 mm. Hg; reduction in heart diameter of 18% or more; correction of T_1 inversion; disappearance of severe retinopathy. Most of these patients were seriously ill and had failed to respond to other forms of treatment. The average time for a marked fall in blood pressure on the diet was three to four months. Of 520 patients, 286 had normal T waves in lead I and 102 abnormal ones before and after treatment; in 122 cases an inverted T_1 wave became upright and in 10 an upright one showed inversion during treatment. Chest radiography in 286 cases showed that 15 had an increase in heart diameter of about 3%, 146 had a decrease of about 6%, 106 had a decrease of about 14%, and 19 had a diminution in transverse diameter averaging 24%. The improvement in cardiographic pattern, the decrease in heart size, and the disappearance of papillœdema, hæmorrhages, and exudates in the fundi seem to bear little relation to fall in blood pressure and may occur on the diet without such a decrease.

The rice diet contains per 2000 calories, less than 5 g. of fat and about 20 g. of protein derived from rice and fruit and less than 200 mg. of chloride and 150 mg. of sodium. There is a marked decrease in the intake of nitrogen, sodium, chloride, and sulphate. Whereas in starvation and in protein deficiency the body uses its own protein with an increase in the blood level of non-protein nitrogen and urea nitrogen, on the rice diet urea and non-protein nitrogen levels decrease. Although salt intake is limited and serum chloride level does fall, restriction of protein in the diet outweighs this effect and protects against azotæmia. A high cholesterol level in the blood, which is often believed to be an important factor in vascular disease, almost invariably falls (by an average of 74 mg. per 100 ml. in 363 patients) on the rice diet.

T. Semple

Penicillin and Caronamide in Resistant Subacute Bacterial Endocarditis. C. H. STUART-HARRIS, J. COLQUHOUN, and J. W. BROWN. *Lancet*, **1**, 99–101, Jan. 15, 1949.

The authors describe 3 cases of subacute bacterial endocarditis in which combined treatment with caronamide and penicillin was effective, after treatment with penicillin alone had been followed by relapse in 2 cases—in one on 3 occasions. In 2 of the cases it was shown that the level of penicillin in the serum was considerably increased by the administration of caronamide and this probably was the factor leading to success of combined therapy. No serious toxic effects were observed but all the patients complained of nausea, and fever and leucopenia were observed in one; there was some sacral œdema in another, suggesting a temporary toxic effect on the renal function, though this has generally not been found in normal subjects.

Maurice Campbell

On the Mode of Formation of Lambl's Excrescences and their Relation to Chronic Thickening of the Mitral Valve. F. R. MAGAREY. *J. Path. Bact.*, **61**, 203–208, April, 1949.

Two hundred and fifty mitral valves were examined at necropsy in a series of cases from which only those of active rheumatic or bacterial endocarditis were excluded.

Lambl's excrescences were not found in subjects less than one year old and became increasingly common with age, being present in every patient over 60. This is a point against their being of congenital origin. On the mitral valve they occur singly or in groups on the auricular surface, chiefly along the line of closure. Shape varies, but they are usually fusiform and 5 or 10 mm. in length. They occur on apparently healthy valves, but are more numerous on vascularized and thickened cusps. Some of the fibrin deposits had lifted at one end and were undergoing organization. This is probably the way in which Lambl's excrescences are formed. Possibly the progressive organization of fibrin in rheumatic carditis leads to formation of rheumatic nodules on the cusps and later to stenosis of the mitral valve.

Peter Harvey

The Role of Desiccated Thyroid and Potassium Iodide in the Cholesterol-induced Atherosclerosis of the Chicken. D. DAUBER, L. HORLICK, and L. N. KATZ. *Amer. Heart J.*, **38**, 25–33, July, 1949. 1 fig., 20 refs.

A high-cholesterol diet in chickens raised their blood cholesterol level. Administration of desiccated thyroid tissue prevented this increase, but potassium iodide augmented it. The same diet induced atherosclerosis, but, whereas administration of desiccated thyroid tissue protected the chickens against this change, the action of potassium iodide was variable.

R. T. Grant

Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding. A. STEINER, F. E. KENDALL, and M. BEVANS. *Amer. Heart J.*, **38**, 34–42, July, 1949. 6 figs., 12 refs.

The serum cholesterol content in 3 dogs given thiouracil (1 g. daily) for over a year was doubled but necropsy showed no atherosclerosis. In 2 dogs given cholesterol (10 g. daily) for 16 months, the serum cholesterol level was trebled, but only minimal atherosclerosis in one case was found post mortem. However, in 2 dogs given both cholesterol and thiouracil, the serum cholesterol content was increased sixfold and eightfold respectively. At

necropsy both showed severe lesions which were very similar in distribution and in histology to those found in human atherosclerosis. *A. S. Dixon*

Plasma and Blood Infusion Following Myocardial Infarction. J. J. SAMPSON and I. M. SINGER. *Amer. Heart J.*, **38**, 54–68, July, 1949.

Acute myocardial infarction may be followed by a shock-like state of pallor, sweating, and hypotension, the severity of which is not related to the degree of myocardial infarction, or of congestive failure. The hypotension itself may be harmful in that it reduces irrigation of the remaining coronary bed and may produce relative anoxia of the brain or kidneys. Eleven patients with repeated myocardial infarction were given small blood or plasma transfusions on one or more occasions. Out of a total of 23 infarctions, 18 were treated by transfusion; in 11 cases the patient responded, but in 7 the patient died. Three other patients died suddenly after recovery from "shock," leaving one survival in the series. Response to transfusion was judged by the effect on blood pressure. There was evidence in some cases that further transfusion might have averted death; on the other hand the death of one patient, who had a high venous pressure, was probably hastened. *A. S. Dixon*

A Techinque for Division and Suture of the Patent Ductus Arteriosus in the Older Age Group. N. E. FREEMAN, F. H. LEEDS, and R. E. GARDNER. *Surgery*, **26**, 103–108, July, 1949.

Serious hæmorrhage during the dissection of a patent ductus arteriosus may be due to friability of the ductus wall, which is made more vulnerable by the difficulty of dissecting behind the duct. The latter is liable to be more than usually friable in older people owing to endarteritic changes.

Crafoord controls both pulmonary and systemic blood flow by placing clamps across the aorta and on the side of the pulmonary artery. This has the disadvantage that the distal aortic flow is prevented for a considerable time. Crafoord, however, reports no ill effects upon renal or other functions.

The present authors have employed a method which gives adequate control of both circulations without complete aortic occlusion, a modified Potts-Smith clamp being used to occlude the aortic end of the ductus. The pulmonary flow is controlled by digital pressure on the left pulmonary artery inside the pericardium. The method has been used with success on four dogs and one human subject. *W. P. Cleland*

The Hemodynamic Effects of Sympathectomy in Essential Hypertension. R. W. WILKINS, J. W. CULBERTSON, and M. H. HALPERIN. *Ann. intern. Med.*, **30**, 291–306, Feb., 1949.

The vascular and metabolic effects of surgical splanchnicectomy for hypertension were investigated in a series of Smithwick's own patients by means of direct arterial-pressure estimations with a Hamilton manometer, cardiac output determinations in which the Fick principle was applied and a cardiac catheter used, and hepato-portal blood-flow studies by the bromsulphalein method. When conditions were stabilized after operation, sympathectomy had not altered either the cardiac output or the blood flow to any important organ, which suggested a widespread decrease in peripheral resistance as the effective cause of the fall in blood pressure. The maintained renal blood flow may prove to be an adaptive response to lowered arterial pressure, and this problem is being studied further.

The decrease in splanchnic vasoconstrictor response in the erect position and the reduction of vasopressor overshoots of arterial pressure after sympathectomy were independent of the post-operative level of blood pressure, but the early increase in and later moderation of hepato-portal blood flow produced by sympathectomy was apparently directly related to the blood-pressure level. It is suggested that indirect physical or chemical mechanisms resulting from the direct hæmodynamic effects of splanchnicectomy may, in certain patients, act by producing a subsequent widespread decrease in peripheral resistance, thus leading to the fall in arterial pressure.
J. L. Lovibond

Transient Ventricular Fibrillation. II. The Effects of Gradually Induced Oxygen Deficiency on Patients with Transient Ventricular Fibrillation and on Patients with Periodic Standstill of the Ventricle. S. P. SCHWARTZ, G. C. LEINER, and R. J. MICHTOM. *Amer. Heart J.*, **37**, 918–926, May, 1949.

The effect of induced oxygen deficiency was studied in 2 patients suffering from transient attacks of ventricular fibrillation and in 2 patients with periodic standstill of the ventricles. The subjects rebreathed from a closed circuit until either loss of mental attention and sustained voluntary control, intense cyanosis, or abnormal changes in the type of breathing occurred.

In one patient in whom transient ventricular fibrillation developed during atrioventricular dissociation, progressive oxygen want easily converted a normal sinus rhythm into one of atrioventricular dissociation. In 2 patients further rebreathing during established atrioventricular dissociation increased the auricular rate, and short runs of ventricular fibrillation developed. In 2 patients, known to have syncopal attacks due to periodic standstill of the ventricles, rebreathing accelerated auricular rate and premature ventricular beats appeared. The appearance of these arrhythmias was irregular. It is suggested that anoxæmia is one of the factors responsible for the development of transient seizures of ventricular fibrillation in patients who are subject to such seizures during atrioventricular dissociation. *H. E. Holling*

Catheterization of the Coronary Sinus in Man. J. W. CULBERTSON, M. H. HALPERIN, and R. W. WILKINS. *Amer. Heart J.*, **37**, 942–951, May, 1949.

Four cases are recorded in which, during right heart catheterization, a cardiac catheter was inadvertently pushed into the coronary sinus. The procedure was watched on the X-ray screen, pressure tracings were taken

with a Hamilton manometer, and blood samples were analysed for oxygen.

The appearance of the catheter on the X-ray screen as it passes into the sinus is characteristic. The catheter, instead of passing from the right atrium to the left and downwards through the tricuspid valve moves directly to the left and upward in an oblique direction along the coronary sulcus. It always comes to a full stop at the left border of the heart, and, so long as it is in the sinus, it always follows exactly the same course. The dark venous colour of the blood withdrawn from the sinus is characteristic. The average oxyhæmoglobin saturation of coronary-sinus blood in these 4 cases was found to be 30%, whereas that of mixed venous blood (50 subjects) was found to be 73%. Pressure tracings showed that the mean pressure in the sinus was from 0 to 15 mm. Hg; the tracings differed from those obtained in the atrium in that the curves ranged slightly higher and showed three waves of vibrations instead of the characteristic atrial pulses. *H. E. Holling*

Kymographic Demonstration of the Systolic Expansion of the Left Auricle in Mitral Disease. D. ROUTIER, R. HEIM DE BALSAC, and L. ALESSANDRIS. *Sem. Hôp. Paris*, **26**, 60–71, Jan. 6, 1950.

The authors describe the use of radioscopy and kymography in the demonstration of systolic expansion of the left auricle in 190 cases of mitral disease. They attribute the auricular expansion to regurgitation of blood during ventricular contraction.

The systolic auricular expansion was particularly marked in cases of arrhythmia and in the presence of ventricular enlargement, and was observed both in the presence of a systolic bruit and in cases of clinically pure mitral stenosis. On the other hand, a systolic bruit might be present without demonstrable auricular expansion, the absence of which does not, therefore, exclude mitral regurgitation, which may be insufficient to dilate the auricle, but nevertheless be sufficient to cause a vibration of the valves which manifests itself in the bruit. However, the extent of the auricular expansion when present provides a rough indication of the volume of blood regurgitated and may thus serve as a guide in the assessment of progress. *A. Orley*

Ætiology and Treatment of Auricular Flutter. D. H. MAKINSON and G. WADE. *Lancet*, **1**, 105–108, Jan. 21, 1950.

Over a 5-year period, 16 cases of auricular flutter were found in a total of 9458 patients subjected to electrocardiographic examination. Careful exclusion of cases of "impure flutter," in which the rhythm was not strictly regular may be responsible for the low incidence of this irregularity as compared with other published series. For purposes of analysis of aetiology, a number of additional cases from private practice were included, making a total of 36 cases, of which 14 were classified as rheumatic in origin, 13 as degenerative heart disease, and 9 as "miscellaneous" in origin including doubtful cases of rheumatism (2), cases of congenital heart disease (2), convalescence from severe illness (2), thyrotoxicosis (1), and rheumatoid arthritis (1), and one case in which no other evidence of disease was detected. The incidence was greatest in the fifth and sixth decades, and before this age rheumatism was the dominant causative factor. There were 29 males to 7 females, this sex distribution being ascribed to the special liability of the male to degenerative cardiovascular disease.

Digitalis was used alone in treatment in 14 cases, normal rhythm being induced in 8 (relapsing subsequently in 2), fibrillation supervening in 4, and flutter persisting in 2. In 9 cases quinidine was given after initial treatment with digitalis, but restored normal rhythm in only 1 of the 4 cases in which fibrillation had been induced and in none of those in which flutter persisted. Quinidine alone restored normal rhythm in 1 of 3 cases thus treated. In those cases which reverted to fibrillation on digitalis therapy there was a close correlation between the time required to induce fibrillation and the dosage of digitalis: 3 grains (0·2 g.) of the powdered leaf thrice a day induced a change of rhythm within 4 days, but if only 2 or 3 grains was given daily periods of treatment of up to 3 months were required. The waves of auricular activity in flutter are best demonstrated electrocardiographically in lead II or lead III, but sometimes better records are obtained with leads from the right præcordium. *J. McMichael*

Acute Serofibrinous Pericarditis of Undetermined Cause. A Study of Twenty-seven Cases. R. L. LEVY and M. C. PATTERSON. *Amer. J. Med.*, **8**, 34–45, Jan., 1950.

The authors describe 27 cases of acute pericarditis of obscure ætiology encountered during a period of 15 years. In 23 there was a history of preceding respiratory tract infection, and it is suggested that these conditions may have been due to virus infection. In other cases the pericarditis was thought to be an allergic reaction to bacterial infection of the throat or nasal sinuses.

The course of the attack varied but all patients recovered completely without sequelæ. Follow-up examinations 6 months to 15 years later revealed no evidence of heart disease in any case. The differential diagnosis from tuberculous and rheumatic pericarditis, and from pericarditis accompanying myocardial infarction, is discussed. Electrocardiography is of assistance in distinguishing the last condition. It is noteworthy that the prolongation of the P–R interval so often seen in acute rheumatism was never observed.

Treatment with sulphonamides, penicillin, and streptomycin seemed to exert no appreciable effect on the course of the disease. The authors suggest that aureomycin treatment would be worth trying. *John Forbes*